**University of Alberta**

# Improving Asthma Care in a Rural Setting: The Better Respiratory Education and Asthma Treatment in Hinton and Edson (BREATHE) Study

by

***Theresa Lynn Charrois*** ©

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requirements for the degree of
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in

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*"The more that you read, the more things you will know. The more that you learn, the more places you'll go."*

- Dr. Seuss, 1904-1991

***For my boys, Jeff and Jack***

# Abstract

Overuse of beta-agonists is a risk factor for poorly controlled asthma. Pharmacists are able to identify high-risk patients through refill information and initiate community-management opportunities for these patients. The BREATHE study was a randomized, controlled trial with high-risk asthma patients. The primary objective was to determine the effect of an education and referral program initiated by community pharmacists, on asthma control, as measured by the Asthma Control Questionnaire. Secondary objectives included determining the effect of this program on hospital events, inhaled corticosteroid use, courses of oral steroids and lung function. There was no significant difference found in asthma control between usual care and intervention at 6-months. There were no differences in the secondary endpoints, however the courses of oral steroids prescribed did approach statistical significance (p=0.08) favouring the intervention. Although no differences were found, this model offers a unique management strategy for rural asthma patients, using a multidisciplinary, community-based approach.

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Finally I need to thank my immediate family. Jack, you offer me the best distraction a grad student could want. Your smile and unconditional love make every day worthwhile. Jeffrey, as someone once said, it is not easy being married to a grad student. You have made it easy for me to complete this journey. You have shown me strength and perseverance, and have always been my biggest supporter. I love you.

## Table of Contents

CHAPTER 1 BACKGROUND AND RATIONALE ..... 1

1.1 Epidemiology of asthma ..... 1
  1.1.1 Prevalence ..... 1
  1.1.2 Incidence ..... 3
  1.1.3 Morbidity ..... 3
    1.1.3.1 Health service utilization ..... 3
    1.1.3.2 Asthma attacks ..... 4
    1.1.3.3 Health-related quality-of-life ..... 4
  1.1.4 Mortality ..... 5

1.2 Asthma Treatment ..... 5
  1.2.1 Treatment Goals ..... 6
  1.2.2 Treatment Guidelines ..... 7
  1.2.3 Medications ..... 7
    1.2.3.1 Inhaled corticosteroids ..... 8
    1.2.3.2 Short-acting beta-agonists ..... 9
    1.2.3.3 Add-on therapy ..... 9
  1.2.4 Other Management Tools ..... 9
    1.2.4.1 Environmental controls ..... 9
    1.2.4.2 Asthma education ..... 9
    1.2.4.3 Written action plans ..... 10

1.3 Care Gaps ..... 12
  1.3.1 Inhaled Corticosteroid Underuse ..... 12
  1.3.2 Education and Written Action Plans ..... 12
  1.3.3 Overestimation of Control ..... 13

1.4 Pharmacist Interventions ..... 14
  1.4.1 Community Pharmacy Interventions ..... 14
  1.4.2 Pharmacist Intervention Studies in Asthma ..... 15

CHAPTER 2 METHODS ..... 21

2.1 Overview of Study Design ..... 21

2.2 Objectives ..... 21
  2.2.1 Primary Objective ..... 21
  2.2.2 Secondary Objectives ..... 21

2.3 Sample ..... 21
  2.3.1 Recruitment ..... 22
    2.3.1.1 Community pharmacy recruitment ..... 22
    2.3.1.2 Hospital recruitment ..... 22
    2.3.1.3 Eligibility ..... 22

2.3.2 Sample Size ........................................ 23

**2.4 Randomization** ........................................ **23**
  2.4.1 Randomization ........................................ 23
  2.4.2 Stratification ........................................ 24
  2.4.3 Blocks ........................................ 24

**2.5 Study Groups** ........................................ **24**
  2.5.1 Usual Care ........................................ 24
  2.5.2 Intervention ........................................ 24

**2.6 Follow-up** ........................................ **25**
  2.6.1 Usual Care ........................................ 25
    2.6.1.1 Follow-up by pharmacist ........................................ 25
    2.6.1.2 Follow-up by respiratory therapist ........................................ 26
  2.6.2 Intervention ........................................ 26
    2.6.2.1 Follow-up by pharmacist ........................................ 26
    2.6.2.2 Follow-up by the respiratory therapist ........................................ 26

**2.7 Data Collection** ........................................ **26**
  2.7.1 Case Report Forms ........................................ 26
  2.7.2 Data Management ........................................ 27

**2.8 Pharmacist Training and Support** ........................................ **27**
  2.8.1 Training Program ........................................ 27
  2.8.2 Ongoing Support ........................................ 28

**2.9 Ethics and Confidentiality** ........................................ **28**
  2.9.1 Ethics Approval ........................................ 28
  2.9.2 Patient Confidentiality ........................................ 29

**2.10 Outcome Measures and Data Analysis** ........................................ **29**
  2.10.1 Outcome Measures ........................................ 29
  2.10.2 Statistical Analysis ........................................ 29

**2.11 Implementation of Study Protocol** ........................................ **31**

**2.12 Design Issues** ........................................ **32**
  2.12.1 Usual Care ........................................ 32
  2.12.2 Unit of Randomization ........................................ 32
  2.12.3 Primary Outcome ........................................ 33
  2.12.4 Differential Follow-up ........................................ 34
  2.12.5 Definition of High risk ........................................ 34

**CHAPTER 3 RESULTS** ........................................ **35**

**3.1 Patients Randomized** ........................................ **35**

3.1.1 Patients Screened ........ 35
3.1.2 Patients Randomized by Site ........ 37
3.1.3 Early Withdrawals ........ 37

**3.2 Baseline Characteristics ........ 38**
3.2.1 Demographics and Asthma History ........ 38
3.2.2 Smoking History ........ 40
3.2.3 Asthma Triggers ........ 41
3.2.4 Asthma History ........ 43
3.2.4.1 Asthma exacerbations ........ 43
3.2.5 Medications ........ 43

**3.3 Primary Endpoint ........ 45**
3.3.1 Change in ACQ from Baseline to 6-months ........ 45
3.3.1.1 Age and change in ACQ ........ 49
3.3.1.2 Gender and change in ACQ ........ 51
3.3.1.3 Site and change in ACQ ........ 52
3.3.1.4 Regression model for change in ACQ ........ 54

**3.4 Secondary Endpoints ........ 57**
3.4.1 Inhaled Corticosteroid Use ........ 57
3.4.2 Forced Expiratory Volume in 1 Second ($FEV_1$) ........ 57
3.4.3 Courses of Oral Steroids ........ 59
3.4.4 ED visits and Hospitalizations ........ 63

**3.5 Education Provided ........ 65**
3.5.1 Pharmacist Provided Education ........ 65
3.5.2 RT-Provided Education ........ 66

**3.6 Recommendations Made ........ 67**

**3.7 Follow-up Visits ........ 69**
3.7.1 Pharmacist Follow-up Visits ........ 69
3.7.2 RT Follow-up Visits ........ 69

**3.8 Additional Analyses ........ 71**
3.8.1 Analysis of Patients with Complete Follow-up ........ 71
3.8.2 Analysis of Patients with Written Action Plans ........ 72
3.8.3 Analysis of Primary Outcome as a Before-After Design ........ 74

**3.9 Summary of Results ........ 74**

**CHAPTER 4 DISCUSSION AND CONCLUSIONS ........ 76**

**4.1 Comparison of BREATHE and A.S.T.H.M.A. Study Patients ........ 77**

**4.2 Primary Outcome ........ 79**

4.2.1 Contamination of Usual Care Group ........ 79
4.2.2 Application ("Dose") of Intervention ........ 81
4.2.3 Losses to Follow-up ........ 83
4.2.4 Sample Size, Power of the Study and Type II Error ........ 84
4.2.5 Imbalance in Study Groups ........ 84
4.2.6 Properties of the ACQ and Definition of Asthma Control ........ 86
4.2.7 Definition of High-risk ........ 88
4.2.8 Summary of Primary Outcome ........ 89

**4.3 Secondary Outcomes ........ 89**
4.3.1 Inhaled Corticosteroid Use ........ 89
4.3.2 Change in $FEV_1$ ........ 90
4.3.3 Courses of Oral Steroids ........ 90
4.3.4 ED visits and Hospitalizations ........ 91

**4.4 Additional Analyses ........ 92**
4.4.1 Analysis of Patients with Complete Follow-up ........ 92
4.4.2 Analysis of Patients with a WAP ........ 93
4.4.3 Before-After Design ........ 93

**4.5 External Validity and Other Limitations ........ 93**

**4.6 Unique Design Aspects ........ 95**
4.6.1 Rural, Community-Based ........ 95
4.6.2 Multidisciplinary ........ 96
4.6.3 Pharmacist-Initiated ........ 96
4.6.4 High-risk Patients ........ 96

**4.7 Implications and Future Research ........ 97**
4.7.1 Rural Health Issues ........ 97
4.7.2 Application to Other Disease States ........ 98
4.7.3 Qualitative Study of Pharmacist Investigators ........ 98

**4.8 Conclusions ........ 99**

**REFERENCE LIST ........ 100**

**APPENDIX 1: RECRUITMENT SCRIPT ........ 114**

**APPENDIX 2: CONSENT FORMS ........ 116**

**APPENDIX 3: WRITTEN ACTION PLAN ........ 121**

## List of Tables

Table 1.1: Asthma control as defined by the Canadian Asthma Consensus Guidelines ..... 6
Table 1.2: Meta-analysis of self-management versus usual care ..... 11
Table 1.3: Comparison of PEF self-management and symptom self-management (44) ..... 11
Table 1.4: Primary outcomes in Weinberger community pharmacy study (82) ..... 16
Table 1.5: Outcomes in the McLean community-pharmacy asthma study (84) ..... 18
Table 3.1: Number of patients randomized by each pharmacy ..... 37
Table 3.2: Early withdrawals from BREATHE ..... 38
Table 3.3: Demographic information and asthma history of BREATHE participants collected at baseline ..... 39
Table 3.4: Smoking status at baseline ..... 41
Table 3.5: Identified provocative factors at baseline ..... 42
Table 3.6: Medications prescribed at baseline ..... 44
Table 3.7: Comparison of change in ACQ from baseline to 6-months and baseline to 2-months ..... 48
Table 3.8: Mean change in ACQ stratified by age ..... 50
Table 3.9: Mean change in ACQ stratified by gender ..... 52
Table 3.10: Comparison of change in ACQ stratified by site ..... 54
Table 3.11: Linear regression model for change in ACQ ..... 55
Table 3.12: Adjusted linear regression model for factors significantly different at baseline ..... 56
Table 3.13: Inhaled corticosteroid use at baseline and 6-months ..... 57
Table 3.14: Mean change in $FEV_1$ from baseline to 6-months ..... 58
Table 3.15: Comparison of mean $FEV_1$ at baseline, 2-months and 6-months ..... 59
Table 3.16: 2x2 table of number of patients who received a short-course of oral steroids during study period ..... 62
Table 3.17: Logistic regression model for courses of oral steroids ..... 62
Table 3.18: 2x2 table of ED visits / hospitalizations post-randomization ..... 65
Table 3.19: Logistic regression model for ED visits / hospitalizations ..... 65

Table 3.20: Pharmacist-provided education throughout the study (n=36)..........66
Table 3.21: RT-provided education throughout the study (n=36)........................67
Table 3.22: Recommendations made by pharmacist (n=36) ..............................68
Table 3.23: Completed follow-up with the pharmacist ......................................69
Table 3.24: Completion of follow-up with the RT ..............................................70
Table 3.25: Number of patients completing 6-month RT and pharmacist follow-ups.....................................................................................................70
Table 3.26: Comparison of change in ACQ from baseline to 6-months in patients who completed 6-month RT visit.................................................................71
Table 3.27: Comparison of change in ACQ from baseline to 6-months in patients who completed both 6-month RT and pharmacist follow-up ........................72
Table 3.28: Linear regression model controlling for written action plans............74
Table 4.1: The Global Initiative for Asthma definitions of asthma control...........87

## List of Figures

Figure 1.1: Prevalence of physician-diagnosed asthma by age and sex, Canada, 1998/99 ..... 1

Figure 1.2: Asthma Treatment Algorithm ..... 8

Figure 3.1: Patients screened and randomized ..... 36

Figure 3.2: Histogram of change in ACQ in intervention patients ..... 46

Figure 3.3: Histogram of change in ACQ in usual care patients ..... 47

Figure 3.4: Change in ACQ (+ SE of the mean) from baseline to 6-months in UC and intervention group ..... 49

Figure 3.5: Mean change in ACQ (+ SE of mean) stratified by age ..... 50

Figure 3.6: Mean change in ACQ (+ SE of mean) stratified by gender ..... 51

Figure 3.7: Mean change in ACQ (+ SE of mean) by site ..... 53

Figure 3.8: Mean $FEV_1$ (+SE) at baseline, 2-months and 6-months ..... 58

Figure 3.9: Distribution of number of courses of oral steroids prescribed over 6-months in intervention patients ..... 60

Figure 3.10: Distribution of number of courses of oral steroids prescribed over 6-months in usual care patients ..... 61

Figure 3.11: Number of ED visits / hospitalizations up to 1-year post-randomization in intervention patients ..... 63

Figure 3.12: Number of ED visits / hospitalizations up to 1-year post-randomization in usual care patients ..... 64

Figure 3.13: Comparison of mean change in ACQ (+ SE of mean) in patients with and without a WAP ..... 73

# Chapter 1 Background and Rationale

Asthma remains a difficult to manage disease that afflicts many Canadians. There are a number of opportunities available for research into novel asthma management strategies.

## 1.1 Epidemiology of asthma

### 1.1.1 Prevalence

Approximately 5% of adults and almost 10% of children in Canada have been diagnosed with asthma (1;2). In Alberta the overall prevalence in persons over 12 years of age is reported at 8.9% (3).

Figure 1.1 shows how prevalence changes as the population ages. The high prevalence in young boys is not maintained into adulthood. In females the highest prevalence is during adolescence and remains higher than males into adulthood (4).

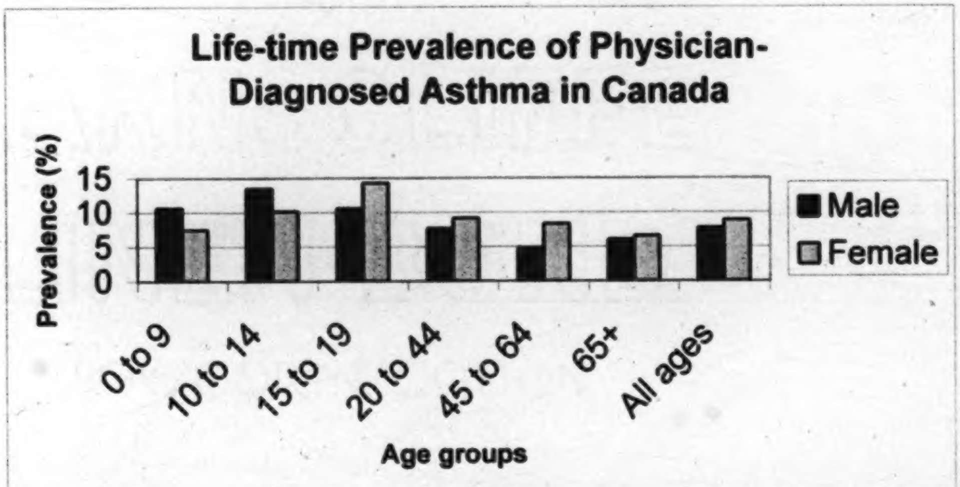

Figure 1.1: Prevalence of physician-diagnosed asthma by age and sex, Canada, 1998/99.

Several large, multi-national studies have been conducted to compare prevalence rates between countries. The International Study of Asthma and Allergies in Childhood (ISAAC) and the European Community Respiratory Health Survey (ECRHS) allow for comparisons of prevalence rates between countries and age cohorts (5-8). These studies have demonstrated wide variations in prevalence rates, with the highest rates seen in Western countries.

Asthma prevalence in Western countries appears to have increased over time, with a recent stabilization (1). This trend has been noted in all age groups (1;9;10). A number of factors have been implicated in increasing asthma prevalence, such as increased exposure to indoor allergens and poorer air quality (2;11). Some factors that may be leading to an artefactual increase in asthma prevalence are: increased diagnosis, increased reporting of disease (reporting bias), increased awareness of the disease and methodologic differences in ascertaining asthma prevalence rates (12). However, as both the prevalence of asthma diagnosis and the prevalence of asthma symptoms have increased simultaneously, it is most likely there is a true increase in prevalence (11).

Measuring prevalence presents a challenge because of the evolving diagnosis and classification of asthma. Prevalence varies significantly between studies and populations depending on the definition used, how it is applied to the population and when the study was conducted. Most large epidemiologic studies have investigated asthma prevalence using a questionnaire, therefore asthma prevalence is primarily based on self-report. Some of the validity issues in these epidemiologic studies include: misclassification, selection bias and recall bias (13). A gold standard for defining asthma does not currently exist and the definition of asthma has changed over time. A physician's diagnosis is not a reliable gold standard for epidemiologic studies due to wide variation in diagnostic criteria (14). However, as no current alternative criterion standard is available, clinical assessment remains the standard for use. The difference in definitions between studies makes comparing results from different studies difficult.

### 1.1.2 Incidence

Incidence, as defined by the number of new cases occurring in an at-risk population during a specified time period, is even more difficult to define in asthma than is prevalence. Since the incident date of the onset of asthma symptoms is difficult to define, measuring disease incidence is difficult. However, some investigators have attempted to describe incidence rates, and have reported rates of up to 3.9% per year (15).

### 1.1.3 Morbidity

Morbidity from asthma can be defined in several ways. Events commonly associated with asthma morbidity are asthma attacks which lead to lost time in work/school, physician visits, emergency department (ED) visits and hospitalizations. Visits to EDs and hospitalizations are commonly used indicators of poorly controlled asthma, and asthma-related morbidity.

The measurement of asthma morbidity is difficult, as changes in morbidity measures (such as hospitalizations) may be more reflective of access to health services and asthma management policies, rather than true changes in morbidity. Definitions of morbidity measures may vary between studies, therefore limiting comparability.

#### *1.1.3.1 Health service utilization*

In Canada, 5.3% of people with asthma require hospitalization each year, however there has been a downward trend over the last 10 years (2;16). Hospitalizations contribute significantly to the overall health care costs associated with asthma, which is estimated at $504-648 million (17). The decline in hospitalizations is attributed to improved asthma control, reduced bed availability and increased treatment and discharge from the ED. The number of hospital days per hospitalization has also decreased since the 1980s (2). Up to 28% of patients require an ED visit each year (2).

One of the difficulties with using hospitalizations or ED visits as an outcome in clinical trials is that these events are based on self-referral, resource constraints and regional differences in health service provision. Studies that utilize a before-after design may reflect changes in health-care delivery, not necessarily acute asthma care.

Factors associated with increases in health-care service utilization include: female sex, higher age, lower socioeconomic status, lower educational level, and inappropriate medication use (18;19). Use of inhaled corticosteroids and written action plans (WAP) help to decrease health-care utilization (20;21).

#### *1.1.3.2 Asthma attacks*

Asthma attacks occur frequently in patients with active asthma. Fifty-six percent of people with active asthma have had an asthma attack in the previous 12 months; and of these, 14% have symptoms continuously (2). These attacks can lead to absences from work and school and an inability to perform normal activities. As an objective outcome measure, it is often easier to quantify health-service utilization, rather than defining and measuring self-reported asthma attacks.

#### *1.1.3.3 Health-related quality-of-life*

Another important asthma morbidity measure is health-related quality-of-life (HRQL). Many different, valid, disease-specific measures have been used to quantify HRQL (22;23). It is difficult to determine, however, if changes in these objective measures are related to clinical outcomes, such as hospitalizations.

ED visits and hospitalizations are less common in asthma patients who have higher ratings of HRQL (24).

People with asthma have significantly poorer ratings of health status compared to non-asthmatics (25). Asthmatics who are treated according to the treatment guidelines have significantly better HRQL compared to those who are not appropriately treated (26).

### 1.1.4 Mortality

Asthma death rates in Canada have decreased since the 1980s and have been relatively stable over the last 10 years. The asthma death rate in 1997 was less than 1.5 per 100,000 (2). The most significant decreases in mortality have been in the 15-24 and over-65 age groups. Most of the epidemiologic studies regarding asthma mortality have been done with the age group of 5 to 34 years, as death attributable to asthma is very likely due to asthma, rather than smoking related obstructive diseases (27). Mortality as an endpoint in studies is only reasonable for very large studies, as deaths due to asthma are a relatively rare occurrence.

Several factors have been linked to asthma deaths. Use of nebulized bronchodilators, higher blood concentrations of salbutamol and oral corticosteroids, are linked with asthma deaths (28). These are also indicators of poor control. Factors associated with decreasing the risk of asthma death include WAP (associated with a 70% reduction in death), use of peak flow meters and use of inhaled corticosteroids (28-31).

## 1.2 Asthma Treatment

Effective management of asthma includes both pharmacologic and non-pharmacologic treatments. The management of asthma has evolved as the definition and targets of drug therapy have evolved.

### 1.2.1 Treatment Goals

The primary goal of asthma management is to provide optimal control. Optimal control is defined as absence of respiratory symptoms, absence of need for rescue bronchodilation and normal pulmonary function. This is very difficult to achieve, therefore the attainable goal of asthma management is acceptable control.

As per the Canadian Asthma Consensus Guidelines, acceptable asthma control is defined by the following parameters (32;33):

Table 1.1: Asthma control as defined by the Canadian Asthma Consensus Guidelines

| Parameter | Frequency or value |
|---|---|
| Daytime symptoms | < 4 days / week |
| Night-time symptoms | <1 night / week |
| Physical activity | Normal |
| Exacerbations | Mild, infrequent |
| Absence from work or school | None |
| Need for short-acting beta-agonist | < 4 doses / week (up to 1 dose/day for prevention of exercise induced bronchoconstriction) |
| $FEV_1$* or PEF* | $\geq$ 90% of personal best |
| PEF diurnal variation | < 10 - 15% diurnal variation |

*$FEV_1$=forced expiratory volume in 1 second; PEF=peak expiratory flow

Asthma control is achieved by control of environment, patient education, self-management and appropriate pharmacotherapy. Asthma severity is defined by the medication required to maintain control and the frequency of symptoms.

### 1.2.2 Treatment Guidelines

There have been several different guidelines for the management of asthma, published by a variety of different groups and stakeholders. The National Asthma Education and Prevention Program Expert Panel (NAEPP) developed and updated their guidelines in 2002 (34). Recently both the British Thoracic Society and Canadian Thoracic Society updated their guidelines for asthma management in adults (33;35).

Respirologists, immunoallergists, pediatricians, emergency physicians and family physicians developed the original Canadian asthma consensus report (32). The primary goal was to provide guidelines that would give consideration to achievement and maintenance of optimal asthma control. These guidelines were updated in 2001 and again in 2004 (32;33). Although these are just a few examples of the guidelines available, they show that there is continuing development and reevaluation of asthma guidelines.

### 1.2.3 Medications

As the second step of the management continuum (after environmental control and asthma education), all patients with intermittent to persistent symptoms require prescription with a short-acting beta-agonist, also called "relievers", for as-needed use. Patients with very mild, intermittent asthma may require no further pharmacotherapy.

As asthma severity increases along the continuum, increased drug therapy is generally required in the form of "controller" (preventive) medications. The cornerstone of asthma symptom control is inhaled corticosteroids (32;33). As severity increases, the dose required to maintain control increases (Figure 1.2).

For patients whose asthma is still uncontrolled on moderate to high doses of inhaled corticosteroid, additional therapy may be required. Additional therapy can include long-acting beta-agonists, leukotriene receptor antagonists, anti-allergic inhaled medications, theophylline, ipratropium and oral steroids (32;33).

General principles of asthma pharmacotherapy include using the lowest dose possible to maintain control, and using inhaled medications to reduce systemic absorption and therefore potential side effects (32;33).

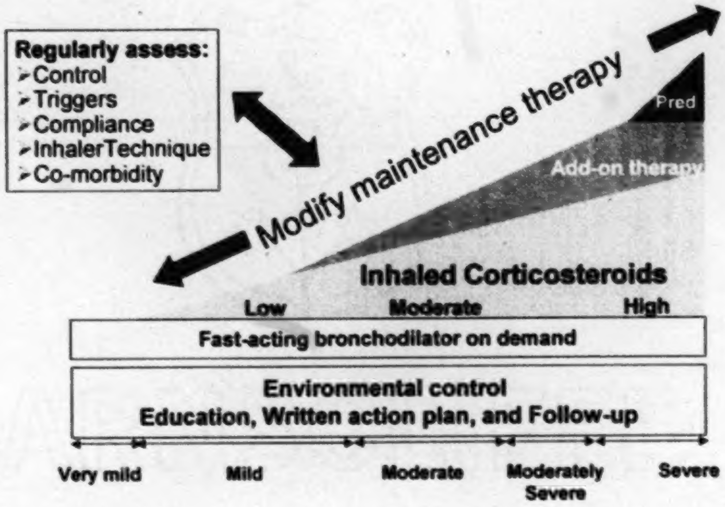
Regularly assess:
Control
Triggers
Compliance
InhalerTechnique
Co-morbidity
Modify maintenance therapy
Pred
Add-on therapy
Inhaled Corticosteroids
Low
Moderate
High
Fast-acting bronchodilator on demand
Environmental control
Education, Written action plan, and Follow-up
Very mild
Mild
Moderate
Moderately Severe
Severe

Figure 1.2: Asthma Treatment Algorithm

### *1.2.3.1 Inhaled corticosteroids*

Inhaled corticosteroids are a mainstay of asthma "controller" drug therapy and are indicated in all but mild cases (32;33). There are a variety of different steroids and delivery devices available for patients. There are still concerns and debate regarding their safety, especially in children, but these drugs remain first-choice anti-inflammatory therapy for most patients (32;33).

#### 1.2.3.2 *Short-acting beta-agonists*

Short-acting beta-agonists are prescribed to all asthma patients as their "reliever" medication. Patients with mild asthma may only require a short-acting beta-agonist. Short-acting beta-agonists are also used for the prevention of exercise-induced bronchospasm. Any patient using their reliever more than 3 times a week should also be on controller therapy (32;33).

#### 1.2.3.3 *Add-on therapy*

Add-on therapy should be considered once patients are well-controlled on their inhaled corticosteroid and want to reduce the dose to reduce the risk of side effects; or receiving high-dose inhaled steroid and still not adequately controlled (32;35).

Generally, long-acting beta-2 agonists are the preferred add-on agents (33;35-37). Other add-on agents include leukotriene receptor antagonists, theophylline, anti-allergic agents, anticholinergics, and rarely, methotrexate, cyclosporine, and gold compounds.

### 1.2.4 Other Management Tools

#### 1.2.4.1 *Environmental controls*

As a standard of asthma therapy, all patients with any severity of asthma should receive education regarding control of environmental allergens and control of provocative factors. Patients should have their triggers identified and education should be given regarding trigger management (32;33).

#### 1.2.4.2 *Asthma education*

Asthma education should be given to all patients, with an emphasis on disease control and maintenance. Education is considered an "essential component" of asthma therapy (32). Education should focus on environmental controls, drug therapy, maintenance of asthma control, monitoring of asthma symptoms, and management of asthma exacerbations.

Studies have shown that written education alone is not adequate for patients. In a Cochrane review of asthma education programs, 12 studies examined the effects of asthma education (information only) on the following outcomes: hospitalization for asthma, emergency department (ED) visits for asthma, unscheduled visits to the physician for the management of asthma, lung function, medication use and asthma symptoms (38). This systematic review showed that only education programs that include a self-management component reduced hospitalization rates or visits to the physician for asthma. In patients with frequent ED visits, asthma education was associated with a reduction in subsequent ED visits for asthma.

Asthma education is an essential component of asthma management and should include development of a WAP, reinforcement of appropriate medication use, and control of provocative factors (32;39).

#### *1.2.4.3 Written action plans*

A WAP is a self-management plan that advises patients to adjust their medications in a predetermined manner, depending on their symptoms and/or peak flow measurements. A WAP can decrease asthma-related morbidity and mortality (39-41). WAPs have been shown to reduce post-discharge morbidity, reduce hospitalizations and ED visits, improve lung function and HRQL (39;42). Self-management plans that include a WAP show greater reduction in hospitalizations than those that do not (Odds Ratio (OR) 0.35, 95% Confidence Intervals (CI) 0.18 - 0.68) (39). The relative risk for hospitalization (in 12 months) for patients not having a WAP was 4.0 (43).

In a Cochrane review of self-management education for adults with asthma, patients who had a self-management plan including a WAP had better morbidity related outcomes than those who received usual care (44). The outcomes from the meta-analysis are included in the table below.

Table 1.2: Meta-analysis of self-management versus usual care

| Outcome (% of subjects) | RR (95% Confidence Intervals) | Number of subjects |
|---|---|---|
| Hospitalizations | 0.64 (0.50, 0.82) | N=2418 |
| ED visits | 0.82 (0.73, 0.94) | N=2902 |
| Unscheduled physician visits | 0.68 (0.56, 0.81) | N=1556 |
| Nocturnal asthma | 0.67 (0.56, 0.79) | N=1136 |

There is still debate as to what type of WAP patients should be given (symptom based versus peak-flow based), however operationally there seems to be little difference between the two (44-46). In a systematic review which included comparison of PEF-based self-management versus symptom-based self-management, no major differences were found in terms of hospitalizations, ED visits, physician visits, days off work and courses of oral steroids.

Table 1.3: Comparison of PEF self-management and symptom self-management (44)

| Outcome | Relative Risk (RR)* (95% CI) |
|---|---|
| Physician visits | 0.93 (0.78 – 1.10) |
| Days off work | 1.96 (0.44 – 4.36) |
| Courses of oral steroids | 1.53 (0.82 – 2.87) |

*<1 favors peak-flow based WAP; >1 favors symptom-based WAP

All patients who require maintenance therapy for asthma control should have a self-management plan (32).

## 1.3 Care Gaps

Less than optimal application of proven efficacious asthma therapies (care gaps) can lead to poor patient outcomes, such as increased health care utilization, decreased quality of life and lost days at work or school (47;48). The identification of these care gaps helps to target certain areas of management for improvement.

### 1.3.1 Inhaled Corticosteroid Underuse

Inhaled corticosteroids are the cornerstone of asthma management as the first-line controller medication for mild persistent to severe asthma (32). Inhaled corticosteroid use has been shown to be much lower than recommended by treatment guidelines for patients with a history of high-risk events and severe asthma. Inhaled corticosteroids are underused, with approximately 30-40% of patients not receiving them (49-51). Underuse of inhaled corticosteroids is associated with poorer outcomes such as increased hospitalizations, ED visits and mortality (52-54). In a retrospective analysis of patients admitted to the ED for asthma, the relative risk (RR) for hospitalization of inhaled corticosteroid users was 0.55, compared to non-users (55). This benefit was consistent across all dose ranges (low to high-dose). Another study found regular use of inhaled corticosteroid was associated with 31% reduction is rate of hospital admissions for asthma (56). Even patients with mild, persistent asthma benefit from regular use of inhaled corticosteroids (57).

Appropriate medication use is imperative for the achievement of asthma control. Regardless of the amount of asthma education administered to a patient, if their asthma is not adequately treated with appropriate medications, they will not be controlled.

### 1.3.2 Education and Written Action Plans

The ASTHMA (Alberta Strategy to Help Manage Asthma) study showed that 55% of patients had no documented education from primary-care physicians (58).

The most common type of education provided was regarding environmental factors (22% of patients). Family physicians report the most significant barrier to providing education to patients is not having appropriate resources available for education (59).

The evidence for use of WAP is strong (considered level 1 evidence in the Canadian Asthma Consensus Guidelines), however implementation in practice is poor (32). In the ASTHMA study of Alberta primary-care clinics, only 2% of asthma patients had a WAP (58). In a survey of physician practices in Canada, only 14% of family physicians report that they develop a WAP with "all" or "most" of their asthma patients (60). In a study conducted in the US, severity level was inversely correlated with the availability of self-management material; patients in most need of having a WAP were less likely to possess one (61) .

### 1.3.3 Overestimation of Control

Another issue in providing asthma patients with optimal asthma therapy is the overestimation of the degree of asthma control, by both health-care providers and patients (62-65). In one study, 77% of family physicians believed they were usually able to achieve asthma control, however evaluation of the patients suggested that only 24% were at acceptable levels of control, as defined by the Canadian consensus guidelines (63).

Patients' perception of asthma control also does not match disease severity. In one survey, 50% of patients who had severe persistent symptoms believed their asthma was controlled (63). This difference between patient perception and actual level of control may be due to a poor understanding of what can be expected from asthma medications and how asthma control is defined.

Overestimation of control is associated with inappropriate treatment (66). Overestimation of a patient's level of asthma control, especially by not ascertaining beta-2 agonist overuse, can potentially lead to fatal outcomes (67-

69). Patients may not be aware of the risks associated with overuse of beta-2 agonists and that control is defined as using less than 4 puffs per week of their reliever.

## 1.4 Pharmacist Interventions

Within the last 15-25 years, the scope of pharmacy practice has changed from a primarily dispensing role to one of a primary health-care provider. Pharmacists are actively involved in therapy assessment, patient education and provision of drug information. As most patients with asthma are in the community and may not regularly see their physician, the community pharmacist may be ideally placed to help identify patients with poor control and help patients achieve better asthma symptom control.

### 1.4.1 Community Pharmacy Interventions

The impact of community pharmacist initiated interventions has been evaluated in a number of studies. The areas that have been studied include asthma, cardiovascular risk reduction, hypertension, and screening programs for many disease states (70-73).

Many of these studies are neither controlled nor randomized and this leads to a lower level of causal inference. There have been few rigorously designed studies, however, conducted in community pharmacy settings. For example, the SCRIP study (Study of Cardiovascular Risk Intervention by Pharmacists) was a large, randomized, controlled trial in a community-pharmacy setting (74). This multi-centre trial showed that pharmacist intervention could improve outcomes in patients with coronary artery disease. The strength of the design and the beneficial outcome serves as a strong basis for future community pharmacy intervention studies.

### 1.4.2 Pharmacist Intervention Studies in Asthma

A number of studies have been published investigating the evolving role of pharmacists and their involvement with community-based asthma patients.

Patient satisfaction with pharmacy services has been studied. Asthma patients are more satisfied with their pharmacy care if they believed their pharmacist was able to help them manage their asthma (75).

Several studies have been conducted that focus on asthma education and the role of the pharmacist. The majority of these studies have been non-experimental or quasi-experimental designs, with small sample sizes and primarily used non-clinical outcomes (76-79). Endpoints utilized in these studies include prescription costs, inhaler technique, peak expiratory flow values and courses of oral steroids (76-79) . Most of these endpoints measure process and structure related outcomes, rather than clinical outcomes (80).

Recently a large trial was published that included asthma patients in a community pharmacy setting (81). Thirty-six drugstores were recruited and divided into clusters of 3 by geographic proximity. The triplets of drugstores were then randomized to 3 treatment groups: pharmaceutical care program (PCP), peak-flow monitoring program (PFM) or usual care (UC). The components of the PCP intervention included a computer program containing patient-specific data (background information, peak flow rates, ED visits, hospitalizations), patient education materials, and pharmacist training on interpreting patient-specific data in patients with reactive airways disease. The patients in the PCP group received a peak flow meter and monthly phone calls to ascertain ED visits, hospitalizations, peak expiratory flow (PEF) rates and compliance rates. The patients in the PFM group received a peak flow meter, instructions for use and monthly calls to obtain PEF rates. Usual care patients received no extra education. Patients with COPD and asthma were included in this study and a total of 1113 patients were enrolled.

Outcome measures included PEF rates, HRQL, medication compliance and hospitalization and ED visits. The sample size was calculated using hospitalization and ED visit data.

Table 1.4: Primary outcomes in Weinberger community pharmacy study (82)

| Outcome | PCP vs. PFM OR (95% CI) | PCP vs. UC OR (95% CI) | Comparison across treatment groups |
|---|---|---|---|
| Hospitalization or ED visits | 2.16 (1.76, 2.63) | 1.08 (0.93,1.25) | <0.001 |

The most interesting finding was that asthma patients in the PCP group were more likely to have a hospitalization compared to the other groups. There was a significant difference found in PEFR between the PCP group and the UC patients (p=0.02), but not between the PCP group and the PFM group (p=0.28). There were no significant group differences in HRQL or compliance. The PCP group did report greater satisfaction with their pharmacist than patients in either of the other groups.

There were several weaknesses identified with this trial. Firstly, the community pharmacy was the unit of randomization, therefore socioeconomic factors, which are important confounders in asthma control, might not be evenly distributed between the study groups. For example, race was significantly different between the treatment groups. Secondly, the intervention was only an educational program, as the pharmacists made no recommendations regarding therapy. Therefore, patients may have been inadequately managed and at higher risk for the primary outcome (ED visits or hospitalizations). The pharmacist could not make recommendations to change this therapy. Thirdly, the endpoint included results for both chronic obstructive pulmonary disease (COPD) patients and asthma patients, a rather heterogeneous group of patients, making it difficult to generalize to one particular group. Finally the pharmacists did not routinely administer the intervention. Pharmacists only accessed study computer data approximately half the time and of these events, only documented actions half the time. Therefore the "dose" (application) of the intervention may have been too low.

Another trial conducted in community pharmacies in British Columbia, Canada has shown promising results (83). The study attempted to demonstrate a significant difference in clinical and economic outcomes in asthma patients who received enhanced pharmaceutical care (EC), compared to usual care (UC). The patients in the UC group were seen in an initial interview, taught proper inhaler technique, given a monthly asthma diary (which included twice daily HRQL questions and recording of ED / hospital visits). A second interview at the end of the study was conducted to reassess symptoms, drug utilization and knowledge. The EC group included all the interventions in the UC group plus teaching of asthma self-management. Regular follow-up appointments were made at least every 3 months. A "control" group was also included in the analysis and this included patients who received no intervention at all (not EC or UC patients).

A total of 631 people consented to be involved in the study. Patients from pharmacies already involved in an asthma program were randomized to EC (n=121) or UC (n=121). None of these patients could be considered for the "control" arm as these pharmacies were already involved in an asthma education program. Another group of pharmacies were then randomized to EC and control (70 in EC and 105 in control) or UC and control (93 in UC and 121 in control). A total of 191 patients were randomized to EC, 214 to UC and 226 to control. There was 'cross-over' of 44 patients from UC to EC (not further explained in the article). A table of patient demographics is not included in the article to accurately ascertain if the complicated randomization scheme and cross-overs had an effect on known prognostic factors and balance between the groups.

Table 1.5: Outcomes in the McLean community-pharmacy asthma study (84)

| **Outcome** | **Result (EC vs. UC)** | **Between group difference (p=value)** |
|---|---|---|
| PEF rates (L/min) | 383 vs. 351 | $p < 0.01$ |
| Symptom scores (0-3 scale) | 0.53 vs. 0.93 | $p < 0.01$ |
| Beta-2 agonist (doses per day) | 1.94 vs. 2.88 | $p < 0.01$ |
| Corticosteroids (doses per day) | 2.37 vs. 2.40 | NS* |
| Hospitalizations (in previous month) | 0.08 vs. 0.16 | NS |
| ED visits (in previous month) | 0.04 vs. 0.21 | NS |
| HRQL (AQLQ*, 1 to 5 scale) | 5.13 vs. 4.40 | $p < 0.01$ |

*NS = not significant, AQLQ = Asthma Quality of Life Questionnaire (85)

Significant differences were found in terms of PEF rates, symptom scores, short-acting beta-2 agonist use and HRQL, all favoring the EC group. The costs (medical visits, ED visits, hospitalizations, prescription drugs, pharmacist fees, days off work/school) were found to be lower in the EC group as compared to the UC group.

There are some issues with design and interpretation of this study. Although the outcomes selected for the study were primarily clinical (symptom scores, hospitalizations, peak flow readings), there were large losses to follow-up, which limit the ability to draw conclusions from this study. Of 631 patients who consented to participate in the study, only 225 patients were analyzed for outcomes. The patients not included in the final analysis may be systematically different from the participants who remained in the study. This study also had some design issues, such as limited generalizability (many of the pharmacists were certified asthma educators), a randomization scheme that included clustering some pharmacists by geographic similarity but not all, and finally utilizing a patient survey that had not been previously validated.

Most recently a small study of self-management delivery by a community pharmacist in England, was published. Participants were recruited through a single pharmacy (86). The participants had to be 18-65 years of age and using inhaled corticosteroids. These patients (n=24) were randomized to intervention or control. The intervention group received a self-management plan and follow-up every week. After 3 months of follow-up the 2 groups were compared with an asthma symptom questionnaire (North of England asthma symptoms scale) (87). The mean scores of the intervention group were significantly improved after follow-up ($p < 0.001$). This study is very promising but is very small, and given that only 1 pharmacist delivered the intervention in 1 town, the generalizability (external validity) is limited. Moreover, treatment was unaltered with respect to medications and baseline dosages, and the self-management plan was PEF based only.

Available evidence suggests that pharmacists may have a positive effect on patient outcomes in asthma. However there is a paucity of well-designed studies that investigate clinical endpoints in asthma patients. It is difficult to interpret or generalize the data from the published literature as the patient populations are diverse, surrogate endpoints are often used and the sustainability of the programs may be difficult. Nevertheless, there are some potential advantages of a community-pharmacy led asthma management program. These advantages include improved pharmacological management of patients, identification of high-risk patients and accessibility of the pharmacist by patients and other health-care professionals. Primary health-care includes a wide array of health professionals, and in order to provide seamless patient care, it is imperative to include all the key players in a patient's asthma care. To build upon the published research on pharmacist interventions in asthma care, we designed a community intervention study that included a multidisciplinary component, a clinical endpoint, both educational and therapeutic interventions, and randomization by patient.

# Chapter 2 Methods

## 2.1 Overview of Study Design

The Better Respiratory Education and Asthma Treatment in Hinton and Edson (BREATHE) study was a prospective, randomized, controlled trial. Patients were randomized to community-management intervention (including pharmacists, respiratory therapist and family physicians) or usual care.

## 2.2 Objectives

### 2.2.1 Primary Objective

The primary objective of the study was to determine the effect of an education, assessment and referral intervention program initiated by community pharmacists on asthma control, as measured by the Asthma Control Questionnaire (ACQ), in patients with poorly controlled asthma (as defined by beta-2 agonist overuse or ED visit / hospitalization in previous 6 months, Section 2.3.1.3).

### 2.2.2 Secondary Objectives

The secondary objectives were to determine the effect of an education, assessment and referral intervention program initiated by community pharmacists on ED visits / hospitalizations, inhaled corticosteroid use, courses of oral steroids and forced expiratory volume in 1 second ($FEV_1$).

## 2.3 Sample

The sample was derived from high-risk asthma patients in Hinton and Edson, Alberta, Canada (from all 4 Hinton pharmacies and 1 pharmacy in Edson). Both communities have populations of less of 10,000 and are over 200 km away from any tertiary care centres. There is one hospital in each town. Hinton is serviced by 4 pharmacies and 13 family physicians. Edson has 3 pharmacies and 9 family physicians.

### 2.3.1 Recruitment

#### *2.3.1.1 Community pharmacy recruitment*

The community pharmacists were responsible for recruiting patients that met the inclusion criteria. They screened patients by their pharmacy refill records to identify overusers of beta-2 agonists (Section 2.3.1.3). They screened these lists periodically over the course of the recruitment phase of the study. Patients that appeared to fit the eligibility criteria were contacted and asked to come into the pharmacy for an initial assessment. The pharmacists used a standardized script when calling their patients to discuss potential recruitment into the study (Appendix 1).

#### *2.3.1.2 Hospital recruitment*

The hospital pharmacist received lists from health records of patients who were admitted to the ED or the hospital for a diagnosis of asthma. The hospital pharmacist contacted these patients to make them aware of the study. Upon receiving verbal consent from the patient, the pharmacist forwarded the name of the patient to the pharmacy where they filled their prescriptions. The patient could refuse to have their name forwarded to their community pharmacy and therefore were not screened for study inclusion. The patients who consented to have their name forwarded to the community pharmacy were contacted for appropriate screening.

#### *2.3.1.3 Eligibility*

The community pharmacist ensured that patients met the eligibility requirements for the study and then obtained written consent (as approved by the University of Alberta Research Ethics Board and Community Research Ethics Board of Alberta, Appendix 2).

Patients were included if they had a diagnosis of asthma (self-reported); were 17-54 years of age; and were considered high risk. High-risk asthma patients were defined as patients who had an ED visit or hospitalization due to asthma in the previous 12 months, or used more than 2 canisters of inhaled beta-2 agonist medication in the previous 6-months.

Patients were excluded if they were not responsible for administering their own asthma medications, were unable to understand English, were unavailable for 6-month follow-up, or did not provide written informed consent.

### 2.3.2 Sample Size

Sample size was calculated based on the standard deviation of scores (SD = 0.54) for change in asthma control using the ACQ, a continuous response variable (88). A clinically significant change in score is considered 0.5 (Juniper EF, personal communication). Therefore, for a power of 90% and a two-tailed alpha of 0.05, the required sample population is 19 patients per group. To account for losses to follow-up and to increase power for secondary endpoints, 35 patients per group were recruited.

## 2.4 Randomization

### 2.4.1 Randomization

Patients were randomized by an internet randomization service through the Epidemiology Coordinating and Research (EPICORE) Centre, University of Alberta. As two sites did not have internet access, opaque envelopes were provided for randomization. The envelopes were all marked and pharmacists were instructed to take each envelope in order. The order was generated by random number list. The process of randomization is important to ensure the study groups are comparable based on both known and unknown prognostic variables.

### 2.4.2 Stratification

Randomization was stratified by centre. This allowed for comparisons between sites and to control for site as a potential confounder in linear regression modeling.

### 2.4.3 Blocks

Randomization was done in blocks of six, therefore the difference in size between the usual care and intervention groups would never be more than 3 patients. This is important, as the sample size is relatively small. Investigators were not made aware of block size.

## 2.5 Study Groups

### 2.5.1 Usual Care

The usual care group was provided with an asthma education booklet and general advice as needed. The asthma education booklet entitled "Take a holiday from your asthma symptoms" (AstraZeneca) was reviewed by asthma educators to ensure up-to-date, accurate information was included. Patients were referred to a respiratory therapist (RT) within one week of randomization for measurement of $FEV_1$.

### 2.5.2 Intervention

As detailed below, subjects assigned to the intervention group received education on asthma, assessment and optimization of drug therapy by the pharmacist, RT referral and physician referral as needed.

The education component included medication teaching on all asthma medications, inhaler technique assessment / education, provision of written asthma education materials and development of a WAP. The WAP was based on the Canadian guidelines and was developed and approved by the local pharmacists, physicians and RT at the first investigators' meeting (32;33)

(Appendix 3). The educational component was initiated by the pharmacists and reinforced by the RT.

Optimization of drug therapy included an assessment of medications by the study pharmacist in concordance with the Canadian asthma guidelines, in particular, ensuring all patients were prescribed an inhaled corticosteroid (32;33). An assessment of adherence to current drug therapy helped determine if the patient was not taking their therapy optimally (i.e. not taking their inhaled corticosteroid regularly, or taking their short-acting beta-2 agonist too often).

Patients were referred to their physician by the pharmacist if therapy adjustments were suggested as determined by the drug therapy assessment. A physician referral form would be faxed to the patient's family physician identifying the patient as high-risk and including any recommendations to the physician regarding current asthma therapy (based on the Canadian guidelines for the treatment of asthma). The fax also included the education being provided to the patient and a copy of the patient's WAP (Appendix 3). As well, patients were referred to the RT within one week of randomization for measurement of $FEV_1$ and reinforcement of education.

## 2.6 Follow-up

### 2.6.1 Usual Care

### *2.6.1.1 Follow-up by pharmacist*

The usual care group had follow-up with the pharmacist at 2 and 6 months. Follow-up included assessment of any outcome events and minimal education (inhaler technique assessment, answer any questions). To address any concerns about provision of "usual care", the patients in the usual care group were offered the intervention (section 2.5.2) after the 6 months of study.

#### *2.6.1.2 Follow-up by respiratory therapist*

Administration of the ACQ by the RT occurred at 2 and 6 months. All patients had $FEV_1$ measured at baseline, and at 2 and 6 months.

### 2.6.2 Intervention

#### *2.6.2.1 Follow-up by pharmacist*

Follow-up for the intervention group included a follow-up telephone call at 2-weeks by the pharmacist to determine if patients in the intervention group made an appointment to see their family physician (if required) and to reinforce education. As well, they ensured that the patient has seen the RT. The intervention group patients had follow-up by the pharmacist at 1, 2, 4 and 6-months for educational reinforcement, medication assessment, assessment of outcome events and reassessment of the WAP.

#### *2.6.2.2 Follow-up by the respiratory therapist*

The RT administered the ACQ at 2 and 6 months (89). The follow-up appointments with the RT included educational reinforcement, measurement of pulmonary function, and reassessment of the WAP in conjunction with the pharmacist.

## **2.7 Data Collection**

### 2.7.1 Case Report Forms

At all follow-up visits, the pharmacists, and when applicable the RT, completed standardized case report forms. Copies of the forms were located in the Manual of Operations. Forms were colour-coded for intervention (cream-coloured) and usual care (white) groups. Epidemiology Coordinating and Research (EPICORE) Centre provided all forms to the centers.

Data collected in intervention included smoking status, triggers, exacerbations, self-monitoring, medications and education provided. This was collected at baseline, 2-weeks, 1-month, 2-months, 4-months and 6-months. In usual care, data collected included smoking status, triggers, exacerbations, self-monitoring and medications. There was no data collected regarding education provided. This was collected at 2 and 6-months in the usual care group.

### 2.7.2 Data Management

EPICORE Centre was responsible for data management of the BREATHE study. All case report forms were faxed to EPICORE Centre on completion and were entered into the database. Queries of any missing/inappropriately filled out data, were faxed out to the sites once entered into the database. Pharmacists and RT were required to keep all study forms until completion of the study at which time the forms were sent to EPICORE Centre and will be kept for 7 years, as per Good Clinical Practice Guidelines.

## 2.8 Pharmacist Training and Support

### 2.8.1 Training Program

Training of pharmacists focused on key concepts of self-management, appropriate drug therapy and patient monitoring. A previously developed and evaluated program called the Asthma Community Pharmacist Training Trial (ACTT) was utilized for the training (90). In the evaluation of the ACTT, pharmacists were randomized to either a traditional, didactic continuing education session, or an interactive, activity and case-based program that focused on patient assessment. After the training session, standardized patient actors using standard patient scenarios approached pharmacists unknowingly in their pharmacy. The study showed that pharmacists who received the ACTT training were significantly better at facilitating plans for the standardized patients, especially regarding the underuse of corticosteroids and overuse of short-acting beta-2 agonists. BREATHE takes this study a step further to quantify this effect on a clinical measure – asthma control.

Unlike most continuing education programs, the training program did not focus on therapeutics. A therapeutic review and update was presented; however, the main focus was patient assessment, patient interviewing and communication skills. Participants spent the afternoon involved in case scenarios with standard patient actors. Feedback, from trained reviewers and actors, was provided about the pharmacist's ability to identify drug related problems in the case, as well as communication and interviewing techniques.

At the end of the training session, the Manual of Operations and an overview of the case report forms were given to the pharmacists. They were shown how to complete the forms and where to find crucial study information.

### 2.8.2 Ongoing Support

Pharmacists, and other team members, were offered a number of support mechanisms during the course of the study. The research coordinator and assistant made periodic site visits to offer support, and ensure compliance with the protocol. Regular investigator meetings were scheduled to maintain contact between the study coordinators and all investigators, and update them on study progress. The study coordinator was available by pager. Newsletters were developed and mailed to all pharmacist investigators, RT and physicians, on a monthly basis. The newsletters included updates regarding the study status, data quality and therapeutic reviews. The pharmacists were also compensated monetarily for their involvement in the study. A payment of $75 per patient was provided to the pharmacy after all outstanding case-report forms and corrections were complete.

## 2.9 Ethics and Confidentiality

### 2.9.1 Ethics Approval

The study protocol and consent forms were approved by the University of Alberta Research Ethics Board and the Community Research Ethics Board of Alberta

(Appendix 2). Patients signed 2 consent forms; one for study participation and one for release of hospital admission data.

### 2.9.2 Patient Confidentiality

All data sent to the research coordinating office was done so with study number and patient initials only. Any information that included patient identifiers was kept at the participating stores and not faxed to EPICORE Centre (i.e., copies of the consent forms).

## 2.10 Outcome Measures and Data Analysis

### 2.10.1 Outcome Measures

The primary endpoint was a comparison of the difference in change in the ACQ scores from baseline to 6 months between intervention and usual care (91). Secondary endpoints included comparison of the number of ED visits and hospitalizations, inhaled corticosteroid use (at baseline and 6 months), number of courses of oral steroid and $FEV_1$ (at baseline, 2 and 6 months) between the intervention and usual care groups.

### 2.10.2 Statistical Analysis

The primary aim of the study was to determine whether subjects receiving pharmacist intervention had improved asthma control, as measured by the ACQ. Also of interest were the differences between the study arms on ED visits and hospitalizations, the use of inhaled steroid, courses of oral steroids and $FEV_1$ values.

Baseline characteristics of the study arms were compared to determine whether randomization was effective and the 2 groups were comparable with regards to known prognostic factors. Univariate analyses were performed using the Student's t-test (for continuous dependent variables) and the Pearson chi-square test (for categorical dependent variables).

The primary outcome variable (change in ACQ between the two groups from baseline to 6 months) was analyzed using the Student's t-test and multiple linear regression to determine the treatment effect. The regression model included any baseline characteristics that do not appear to be balanced and adjusted for any potential confounders. The potential confounders included were age, sex, and site.

The change in $FEV_1$ was compared using the Student's t-test and multiple linear regression for modeling. The proportion of patients on inhaled corticosteroids at 6 months was compared using Chi-square and logistic regression to adjust for confounders (inhaled corticosteroid use at baseline). To compare ED visits and hospitalizations between the two groups, it was first assessed whether the distribution was normal. If the distribution was normal, the data was to be analyzed using the Student's t-test. If the distribution was not normal, the Mann-Whitney U test was used to compare the difference in medians between the groups. Chi-Square and logistic regression were also used to compare the groups using the dichotomous outcome of any ED visits / hospitalizations (yes or no). The courses of oral steroids were analyzed the same way as the ED visits / hospitalizations, after the normality of the distribution was been determined. For the logistic regression model of courses of oral steroids, previous courses of oral steroids were controlled.

All analyses were done using intention to treat principles.

For missing final scores of the ACQ, the last value recorded was carried forward. This is the most conservative approach for dealing with missing data (92). This method assumes there has been no change and that the data is missing at random, i.e., the reason the data is missing is not due to the study or the patient's health status. This method is reproducible unlike other imputation methods (hot / cold-decking) (92). If there was a missing item in the scale, the mean of the available items was imputed.

### 2.11 Implementation of Study Protocol

In order to effectively administer the study protocol, it was decided that all key stakeholders should be involved with the study design. Involvement of all stakeholders was felt to be important for acceptance and is a unique aspect of this study. However, the disadvantage of this approach is the risk of contamination of the usual care group, as all primary health-providers (physicians, pharmacists, and RT) involved in the intervention were included in discussions regarding study design.

An initial meeting was scheduled in Hinton (March 2002) to discuss specifically the study design and outcome measures. Initially the study team had proposed using ED visits and hospitalizations. After discussion with the physicians, it was determined that often the physician offices are used as a walk-in clinic and for urgent care needs. Therefore ED visits and hospitalizations may not accurately reflect all urgent events related to asthma. Therefore the protocol was revised and a measurement of asthma control was used instead as the primary outcome measure.

The development and approval of the WAP was also done in consultation with the stakeholders in the community. A nurse (Heather Sharpe, MN) from the asthma clinic at the University of Alberta who has experience in asthma teaching, led a discussion with physicians and pharmacists regarding how the WAP should be designed and what would be the peak expiratory flow cut-offs for the different zones. The WAP was accepted by the physicians as developed, which gave the pharmacists the autonomy to develop the WAP, with the patient, at the community pharmacy level.

## 2.12 Design Issues

### 2.12.1 Usual Care

Participants randomized to usual might actually receive better pharmacy care than usually provided to asthma patients in the pharmacy setting. Specifically, there is an element of education, in the provision of written materials and assessment of inhaler technique. There is also follow-up and referral to a RT, which is not a standard of care currently in pharmacy practice. Finally, all patients allocated to the usual care group were offered the intervention at the end of the 6-month follow-up.

Any controversy over the ethics of randomization to usual care needs to be balanced with the higher causal inference that can be concluded from the study results and resource implications of advocating a program of care that does not have proven efficacy. In this study, the usual care arm is unlikely to cause harm, as more care than "usual" is being offered.

### 2.12.2 Unit of Randomization

Randomized trials provide the highest level of causal inference. We chose to use the individual patient as the unit of randomization to control for known and unknown confounders. In addition, even though the pharmacies are located in rural areas, there still may be some demographic and socioeconomic differences in the populations served by each pharmacy. As with many chronic diseases, socioeconomic and demographic factors are associated with differences in asthma control, therefore it is important to control for these known and unknown prognostic factors via randomization (93).

The pharmacists involved in the study felt it was unacceptable for them to provide only one arm of care. They are a motivated group of professionals, who all wanted to be involved in the intervention. Although there may be some contamination of the usual care group given this select group of pharmacists, their level of usual care is at a higher level than what is normally provided. There is the potential of blunting of the treatment effect as the usual care group may be "contaminated" by the unblinded clinicians involved in the study providing similar care to both study groups. The pharmacists will have enhanced knowledge after the training sessions which may potentially affect their treatment of usual care patients. To offset this potential blunting of the treatment effect, the "dose" of the intervention provided needs to be high, therefore follow-up and reassessment is critical, and the emphasis on WAP for all intervention patients is essential.

#### 2.12.3 Primary Outcome

The ACQ is a clinically important endpoint, as the patient's actual control of their disease is being measured. The ACQ incorporates both objective and subjective measures of control. Secondarily, the ACQ was selected over ED visits and hospitalizations, as the sample size required was more achievable. In discussion with pharmacists and physicians in Hinton, the rate of hospitalization and ED visits may be lower than anticipated, as the patients use the medical clinics often as a walk-in facility instead of going to ED. This highlights the importance of our preliminary meetings with pharmacists and physicians to learn about local practices. Therefore, by using a continuous variable (ACQ) as the primary endpoint, the sample size required is decreased.

The ACQ is a well-validated scale (94-96). In the primary validation study of the instrument, reliability, responsiveness, evaluative and discriminative properties were studied. As this questionnaire is being used as an evaluative measure in this study, responsiveness is the most important validity measure. The responsiveness of the ACQ in the validation study was high as the measure did not significantly change in the stable group ($p>0.05$) and was significantly able to detect change in the group of patients who deteriorated ($p<0.0001$). It has been used in a number of clinical trials as an outcome measure to evaluate change in asthma control (97-100).

### 2.12.4 Differential Follow-up

The intervention group is followed more closely than the usual care group, and this could potentially lead to surveillance bias or recall bias. We anticipated that it is not just the education and assessment component that will improve asthma control, but the frequent contact with the patients. The differential follow-up is part of the intervention. As the primary endpoint is ACQ, which does not rely on patient recall, the differential follow-up should not directly affect the primary outcome.

### 2.12.5 Definition of High risk

We selected beta agonist overuse as a marker of poor asthma control. There is no standard definition of beta-agonist overuse in the literature or consistent description of what amount of beta-agonist use puts a person at higher risk of morbidity and mortality. Inappropriate beta-agonist use is associated with higher health care utilization (101;102). Our inclusion criteria for beta-agonist overuse far exceeds what is in the current Canadian consensus guideline for the definition of asthma control (< 4 puffs of reliever medication per week, or < 1 inhaler per 6 month period) and therefore should capture high risk patients (32).

Patients who have a prior ED visit or hospitalization have been shown to be at higher risk for a repeat ED visit. In a study of patients with moderate to severe asthma, the OR for repeat ED visits was 2.9 (95% CI 1.8, 4.8) if they had a hospital admission in the previous year (103). In a case-control study examining markers for readmission, an admission in the previous 12 months was associated with a 3 fold-increase for risk of readmission (95% CI, 2.1, 4.2) (104). In a prospective cohort study of patients relapsing within 8 weeks of an acute exacerbation, having made 3 or more visits to the ED in the previous 6 months, independently predicted relapse (Hazard Ratio = 2.3, 95% CI 1.6, 3.4) (105).

In conclusion, both beta-2 agonist overuse and previous ED visit or hospitalizations are predictors of future health-care utilization.

# Chapter 3 Results

## 3.1 Patients Randomized

### 3.1.1 Patients Screened

Potential study participants were screened at both community and hospital pharmacies. The data presented here represents only the patients who had complete screening visits at the community pharmacy. The hospital pharmacist did not collect screening data as the patients were referred to the community pharmacist for the complete screening.

Figure 3.1 shows the number of patients screened and subsequently randomized into the BREATHE study.

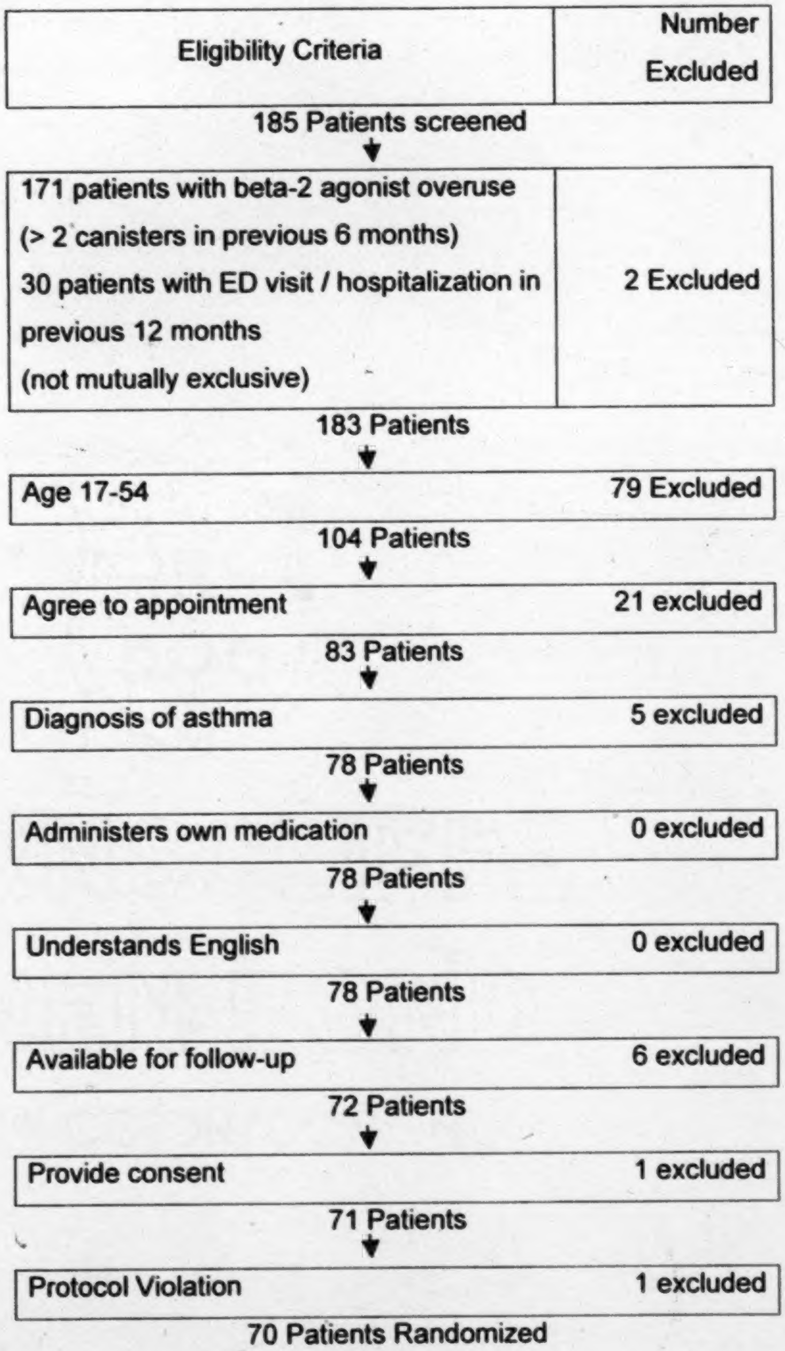
Eligibility Criteria
Number Excluded
185 Patients screened
171 patients with beta-2 agonist overuse
(> 2 canisters in previous 6 months)
30 patients with ED visit / hospitalization in previous 12 months
(not mutually exclusive)
2 Excluded
183 Patients
Age 17-54
79 Excluded
104 Patients
Agree to appointment
21 excluded
83 Patients
Diagnosis of asthma
5 excluded
78 Patients
Administers own medication
0 excluded
78 Patients
Understands English
0 excluded
78 Patients
Available for follow-up
6 excluded
72 Patients
Provide consent
1 excluded
71 Patients
Protocol Violation
1 excluded
70 Patients Randomized

Figure 3.1: Patients screened and randomized

One patient randomized to usual care (UC) did not provide written consent and was therefore considered a "protocol violation". This patient was therefore not included in the analysis. A total of 34 patients were randomized to usual care and 36 to intervention.

### 3.1.2 Patients Randomized by Site

Randomization was stratified by site, to ensure relatively equal numbers of UC and intervention patients at each pharmacy (Table 3.1).

Table 3.1: Number of patients randomized by each pharmacy

| **Site** | **Number of patients randomized N (%)** | **Usual Care (n=34) N (%)** | **Intervention (n=36) N (%)** |
|---|---|---|---|
| Site 1 | 31 (44.3) | 15 (44.1) | 16 (44.4) |
| Site 2 | 11 (15.7) | 5 (14.7) | 6 (16.7) |
| Site 3 | 12 (17.1) | 6 (17.6) | 6 (16.7) |
| Site 4 | 6 (8.6) | 3 (8.8) | 3 (8.3) |
| Site 5 | 10 (14.3) | 5 (14.7) | 5 (13.9) |

The stratified randomization produced equal numbers of UC and intervention patients at each site. Site 1 recruited almost half of the entire study population.

### 3.1.3 Early Withdrawals

As shown in Table 3.2, there were a total of 9 early withdrawals from the study. Seven patients withdrew from the intervention group, and 2 from usual care (UC) (p=0.06, Fisher's Exact Test). The most common reason for withdrawal was the patient no longer wishing to continue (77.8% of withdrawals).

Table 3.2: Early withdrawals from BREATHE

| **Reason for Withdrawal** | **Usual Care (n=34) N (%)** | **Intervention (n=36) N (%)** |
|---|---|---|
| No longer wishes to continue | 1 (2.9) | 6 (16.7) |
| Lost to follow-up | 1 (2.9) | 0 (0) |
| Other reason | 0 (0) | 1 (2.8) |

## 3.2 Baseline Characteristics

### 3.2.1 Demographics and Asthma History

Demographics, prognostic factors and potential confounders were recorded at the baseline visit. These baseline factors were compared to determine if they were similar between the two groups, to assess the effectiveness of randomization (Table 3.3).

Table 3.3: Demographic information and asthma history of BREATHE participants collected at baseline

| | **Usual Care (n=34) N (%)** | **Intervention (n=36) N (%)** | **Difference between groups** |
|---|---|---|---|
| Age | 38.7 years (SE 1.8)* | 35.7 years (SE 1.7) | NS |
| Gender (female) | 18 (52.9) | 19 (52.8) | NS |
| Education Level (achieved high school or higher) | 27 (79.4) | 27 (75.0) | NS |
| Previous pulmonary function test done | 22 (64.7) | 15 (41.7) | $X^2$=3.73, 1df **p=0.05** |
| Determined to have adequate inhaler technique | 30 (88.2) | 24 (66.7) | $X^2$=4.61, 1df **p=0.03** |
| Uses a peak expiratory flow meter | 11 (32.4) | 4 (11.1) | $X^2$=4.67, 1df **p=0.03** |
| Uses a spacer | 8 (23.5) | 8 (22.2) | NS |
| Baseline ACQ score | 1.91 (SE 0.18) | 1.45 ( SE 0.19) | NS |
| **Self-reported asthma morbidity** | | | |
| Unscheduled physician visit in previous 6-months | 18 (52.9) | 10 (27.8) | $X^2$=4.61, 1df **p=0.03** |
| Emergency side-stream in previous 6-months | 5 (14.7) | 4 (11.1) | NS |
| **Asthma morbidity from hospital data** | | | |
| Events 1 year prior to randomization | 9 (26.5) | 6 (16.7) | NS |

NS = non-significant, SE = standard error

Four variables were found to be significantly different between UC and intervention at baseline, including previous pulmonary function testing, adequate inhaler use, home peak flow monitoring and unscheduled physician visits in previous 6-months (Table 3.3). Significantly more usual care patients were determined to have adequate inhaler technique. Also, significantly more usual care patients reported having had prior pulmonary function testing, which is an important diagnostic factor. Usual care patients more frequently reported using a peak expiratory flow meter, which may indicate an increased awareness of asthma symptoms and control. The last statistically significant difference between the two groups at baseline was unscheduled physician visits in the previous 6-months; usual care patients reported significantly more. These four factors will be further explored in the multivariate regression analyses. Other commonly reported prognostic factors (age, gender) were not significantly different between the groups. The baseline ACQ scores were not significantly different at baseline, however the difference in scores does approach the minimal clinically important difference of 0.5.

### 3.2.2 Smoking History

Smoking was defined according to the guidelines used in the National Population Health Survey (106).

a. Current Smokers – includes those who smoked at the time of the interview, and includes daily smokers and non-daily smokers (also known as occasional smokers). Smoking status was determined from the question "At the present time do you smoke cigarettes daily, occasionally or not at all".
b. Former Smokers – includes patient who were not smoking at the time of the interview, and answered "yes" to the question "Have you ever smoked cigarettes at all?" This was then further classified into former daily smokers and former occasional smokers, in response to the question "Have you ever smoked cigarettes daily".

c. Never Smoker – was not smoking at the time of the interview and answered "No" to the question "Have you ever smoked cigarettes at all?"

d. Non-smokers – are former smoker and never smokers combined.

Table 3.4: Smoking status at baseline

| **Smoking Status** | **Usual Care**<br>**(n = 34)**<br>**N (%)** | **Intervention***<br>**(n = 36)**<br>**N (%)** |
|---|---|---|
| **Current Smokers** | 10 (29.4) | 11 (30.6) |
| Daily Smokers | 9 (26.5) | 8 (22.2) |
| Non-daily smokers | 1 (2.9) | 3 (8.3) |
| **Former Smokers** | 10 (29.4) | 9 (25.0) |
| Daily Smoker | 8 (23.5) | 8 (22.2) |
| Non-daily smoker | 2 (5.9) | 1 (2.8) |
| **Never smoker** | 14 (41.2) | 14 (38.9) |

(*data not available for 2 patients in intervention group)

From Table 3.4, most of the study population was non-smokers (67%, includes former smokers and never smokers). There was no significant difference in the 3 categories of smokers between UC and intervention ($X^2$ = 0.100, 2df, p=0.95).

### 3.2.3 Asthma Triggers

There are a number of different provocative factors identified as triggers in asthma. To complete the comprehensive baseline evaluation, patients were asked to characterize what factors triggered their asthma.

Table 3.5: Identified provocative factors at baseline

| Provocative Factor | Usual Care (n = 34)<br>N (%) | Intervention (n = 36)<br>N (%) |
|---|---|---|
| **Indoor Inhalant Allergens** | | |
| Cats | 22 (64.7) | 20 (55.6) |
| Other Animals | 16 (47.1) | 16 (44.4) |
| Dust Mites | 21 (61.8) | 20 (55.6) |
| Molds | 15 (44.1) | 22 (61.1) |
| **Outdoor Inhalant Allergens** | | |
| Environmental | 29 (85.3) | 26 (72.2) |
| **Occupational Allergens** | | |
| Occupational exposure | 16 (47.1) | 11 (30.6) |
| **Irritant Allergens** | | |
| Tobacco smoke | 28 (82.4) | 24 (66.7) |
| Household chemicals | 15 (44.1) | 14 (38.9) |
| Perfume | 18 (52.9) | 17 (47.2) |
| Pollution | 24 (70.6) | 23 (63.9) |
| Wood stove / fireplace | 16 (47.1) | 12 (33.3) |
| **Other Factors** | | |
| ASA / Non-steroidal anti-inflammatory drugs | 8 (23.5) | 3 (8.3) |
| Endocrine | 2 (5.9) | 0 (0) |
| Exercise | 27 (79.4) | 25 (69.4) |
| Food / food additives | 10 (29.4) | 8 (22.2) |
| Gastroesophageal reflux disease | 8 (23.5) | 8 (22.2) |
| Respiratory Virus | 26 (76.5) | 24 (66.7) |
| Weather | 23 (67.6) | 25 (69.4) |
| Other (not previously specified) | 8 (23.5) | 12 (33.3) |

Commonly reported triggers included environmental allergens, tobacco smoke and exercise (Table 3.5). Patients rarely reported experiencing endocrine-induced asthma or ASA/non-steroidal anti-inflammatory triggers.

### 3.2.4 Asthma History

#### *3.2.4.1 Asthma exacerbations*

Asthma morbidity, as defined by unscheduled physician visits, ED visits, hospital admissions and emergency side-stream courses (administered at the physician's office) were assessed at baseline (Table 3.3).

From our initial meetings, it was apparent that some patients used the medical clinics for drop-in treatment; therefore we included the emergency side-stream as an indicator of asthma morbidity, as these patients would have proceeded to the ED if this service was not available through their physicians. Days missed from work or school were also included. Self-reported and hospital admission data was collected.

The hospital data was collected 1 year prior to the date of randomization (as defined by ICD-9 and ICD-10 codes) (see Table 3.3). In the intervention group, there were 6 patients who had at least 1 ED visit or hospitalization 1 year prior to randomization. The number of events per patient ranged from 1-8. In the UC group, 9 patients had an event in the previous year ranging from 1-8 per patient.

From the intervention group, 1 patient had 1 missed work or school in previous 6-months. In UC, 3 patients had missed work or school days ranging in frequency from 1-7 times.

### 3.2.5 Medications

Prescribed asthma-related medications were recorded from pharmacy records and are listed in Table 3.6.

Table 3.6: Medications prescribed at baseline

| **Medication** | **Usual Care (n = 34) N (%)** | **Intervention (n = 36) N (%)** |
|---|---|---|
| **Controller Medications** | | |
| Any inhaled corticosteroid | 26 (76.5) | 25 (69.4) |
| Beclomethasone | 1 (2.9) | 2 (5.6) |
| Fluticasone | 12 (35.3) | 17 (47.2) |
| Budesonide | 6 (17.6) | 3 (8.3) |
| Fluticasone/Salmeterol | 8 (23.5) | 5 (13.9) |
| Budesonide/Formoterol | 2 (5.9) | 3 (8.3) |
| Long-acting beta-2 agonist | 2 (5.9) | 3 (8.3) |
| Other | 2 (5.9) | 3 (8.3) |
| **Reliever Medications** | | |
| Salbutamol | 30 (88.2) | 31 (86.1) |
| Terbutaline | 3 (8.8) | 2 (5.6) |
| Fenoterol | 0 (0) | 0 (0) |
| Other | 4 (11.8) | 3 (8.3) |
| **Oral Steroids** | | |
| Maintenance oral steroid | 1 (2.9) | 1 (2.8) |
| Short-course oral steroid (in previous 6-months) | 11 (32.4) | 12 (33.3) |
| **Other** | | |
| Leukotriene Receptor Antagonist | 4 (11.8) | 9 (25.0) |
| Inhaled anti-allergic | 1 (2.9) | 0 (0) |
| Anticholinergic | 3 (8.8) | 2 (5.6) |
| Theophylline | 3 (8.8) | 0 (0) |
| Ketotifen | 0 (0) | 1 (2.8) |
| Other | 5 (14.7) | 3 (8.3) |

In this high-risk group of patients, 27% were not prescribed an inhaled corticosteroid, as described in Table 3.6. Fluticasone was the most commonly prescribed inhaled steroid, both as a single-entity medication and in combination with salmeterol. Salbutamol was the reliever of choice, prescribed in almost 90% of patients. Approximately 30% of the population were receiving a long-acting beta-2 agonist, either alone or in a combination product. The most commonly prescribed add-on medication was long-acting beta-2 agonists, followed by leukotriene receptor antagonists.

There was no statistically significant difference in the number of patients prescribed inhaled corticosteroid at baseline ($X^2$ = 0.437, df 1, p=0.51). One patient in the intervention group and 2 patients in the UC group were prescribed their inhaled corticosteroid as needed, rather than for regular use. The number of short-courses of oral steroids, as an indicator of asthma control, prescribed in the previous 6-months was also not significantly different between the two groups ($X^2$ = 0.008, df 1, p=0.93).

## 3.3 Primary Endpoint

### 3.3.1 Change in ACQ from Baseline to 6-months

The primary endpoint was calculated by subtracting baseline ACQ score from the 6-month ACQ score. Therefore, a positive number indicates an improvement in asthma control, and a negative number indicates deterioration in asthma control.

The change in ACQ from baseline to 6-months was assessed to determine whether it was normally distributed in the 2 study groups (Figure 3.2 and Figure 3.3).

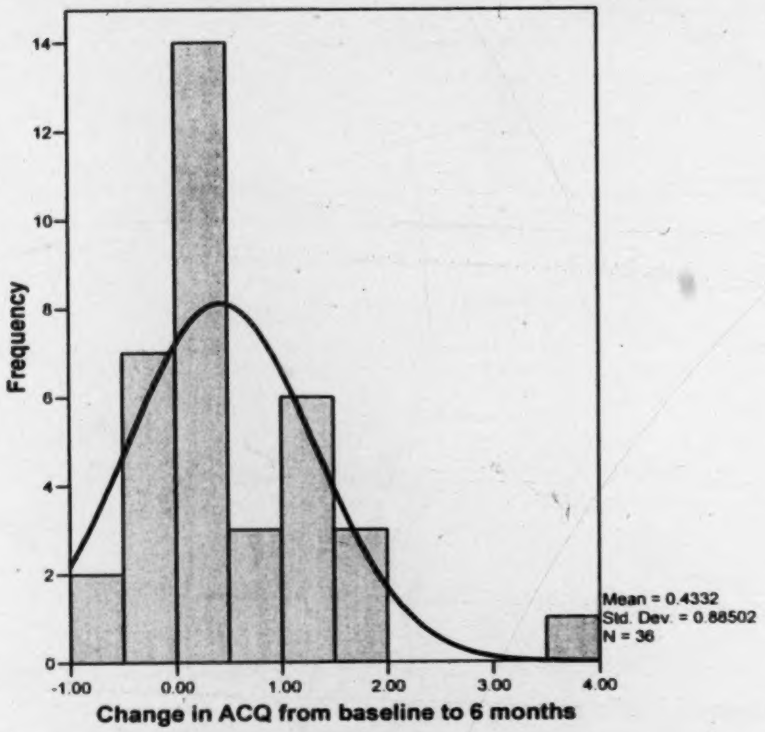

Figure 3.2: Histogram of change in ACQ in intervention patients

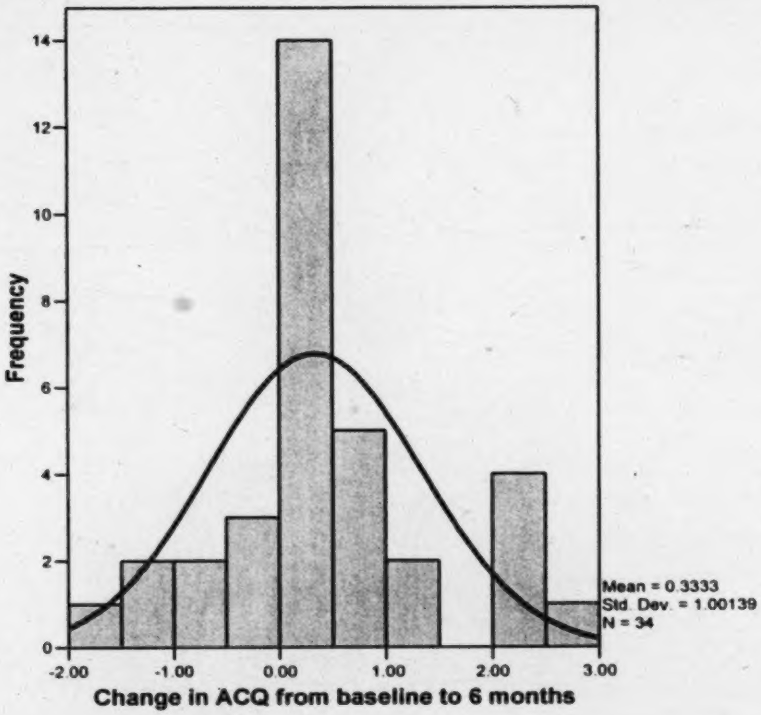

Figure 3.3: Histogram of change in ACQ in usual care patients

As the distributions appear approximately normal, the means of the 2 independent groups were initially compared using the Student's t-test. The primary endpoint was the change between baseline and 6-months. The change between baseline and 2-months was also analyzed. Table 3.7 shows the change in ACQ as measured at both 2-months and 6-months. A total of 30 patients had a value carried forward from either the baseline or 2-month ACQ.

Table 3.7: Comparison of change in ACQ from baseline to 6-months and baseline to 2-months

| | **Usual Care Mean change in ACQ (SE)** | **Intervention Mean change in ACQ (SE)** | **Difference between groups** |
|---|---|---|---|
| Change in ACQ from baseline to 2-months | 0.06 (0.11) | 0.22 (0.11) | t = 1.03, 68 df<br>p=0.31 |
| Change in ACQ from baseline to 6-months | 0.33 (0.17) | 0.43 (0.15) | t = -0.443, 68 df<br>p=0.66 |

(SE = standard error)

The change in ACQ was not significantly different between UC and intervention groups at 2-months or at 6-months (Table 3.7). There was a somewhat greater change in ACQ at 6-months as compared to the change at 2-months.

The mean change in ACQ from baseline to 6-months is displayed graphically in Figure 3.4.

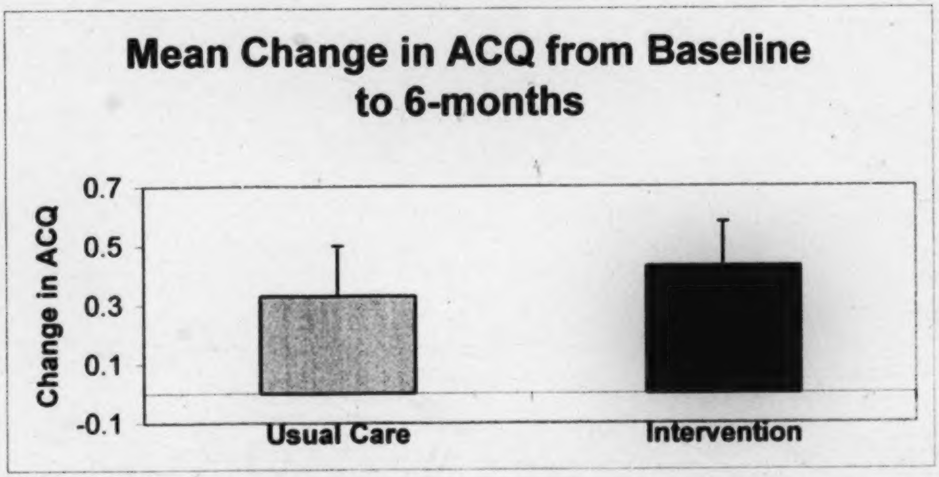

Figure 3.4: Change in ACQ (+ SE of the mean) from baseline to 6-months in UC and intervention group

To explore what factors may influence the change in ACQ, further descriptive analyses were conducted with potential confounders.

### *3.3.1.1 Age and change in ACQ*

Age is a potential confounder as patients of higher age are at increased risk of morbidity. The data was split into 2 groups, <30 years or $\geq$30, and compared with regards to change in ACQ.

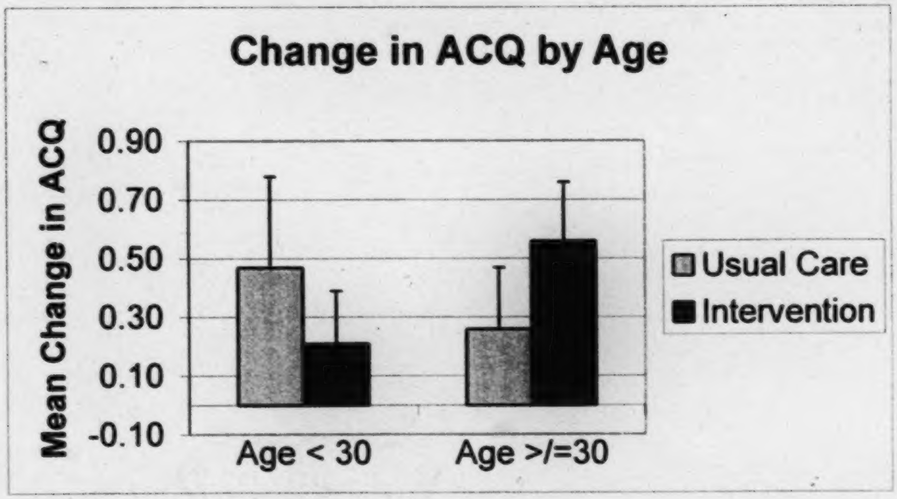

Figure 3.5: Mean change in ACQ (+ SE of mean) stratified by age

From Figure 3.5, it appears that there was a greater change in ACQ in older patients in the intervention group. In UC the change in ACQ was greater with younger patients.

To determine if there was a statistically significant difference between usual care and intervention categorized by age, we compared the means of change in ACQ between the UC and intervention groups (Table 3.8).

Table 3.8: Mean change in ACQ stratified by age

| **Variable** | **Usual Care Mean change in ACQ (SE)** | **Intervention Mean change in ACQ (SE)** | **Difference between groups** |
|---|---|---|---|
| Age < 30 | 0.49 (0.27) | 0.29 (0.15) | t = 0.707, 32 df<br>p=0.49 |
| Age ≥ 30 | 0.23 (0.23) | 0.71 (0.31) | t = -1.28, 32 df<br>p=0.21 |

There is not a significant difference in change in ACQ when stratified by age. Patients both < 30 and ≥ 30 have a similar change in ACQ over the course of the study.

### *3.3.1.2 Gender and change in ACQ*

The mean change in ACQ was also compared by gender to ascertain any differences between the groups, based on a potential confounding factor. Females tend to be at higher risk of asthma-related morbidity.

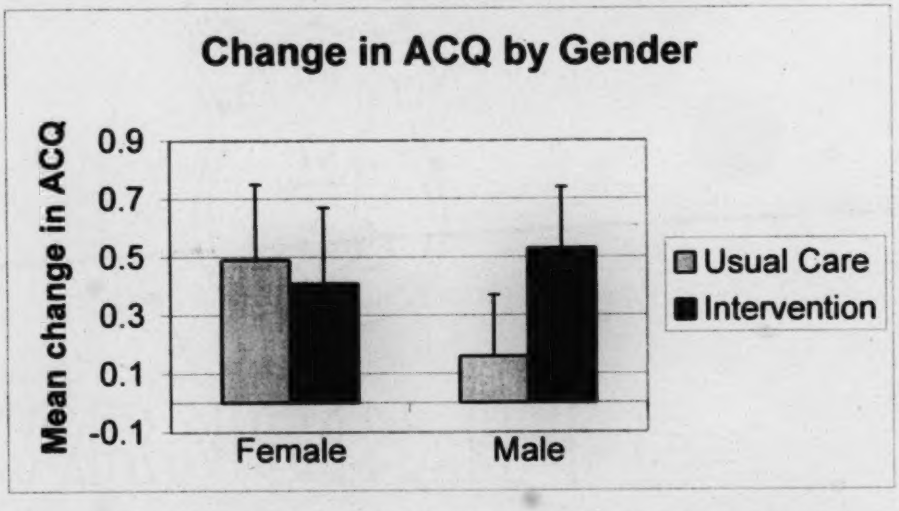

Figure 3.6: Mean change in ACQ (+ SE of mean) stratified by gender

From Figure 3.6, it appears there may be a difference in change in ACQ in males between UC and intervention. This was tested for statistical significance.

Table 3.9: Mean change in ACQ stratified by gender

| Variable | Usual Care Mean change in ACQ (SE) | Intervention Mean change in ACQ (SE) | Difference between groups |
|---|---|---|---|
| Female | 0.49 (0.26) | 0.41 (0.17) | t = 0.263, 35 df<br>p=0.79 |
| Male | 0.16 (0.21) | 0.53 (0.29) | t = -1.02, 29 df<br>p=0.32 |

Using the Student's t-test, it was concluded that there were no statistically significant differences between treatment groups, based on gender (Table 3.9). Therefore, it is not anticipated that gender will contribute to the linear regression model.

#### *3.3.1.3 Site and change in ACQ*

Randomization was stratified by site so that each pharmacy would have equal numbers of patients randomized to usual care and intervention. Site may be a potential confounding factor as it reflects differences in pharmacists, practice environment, application of the intervention, and potentially differences in patient population with regards to socioeconomic status.

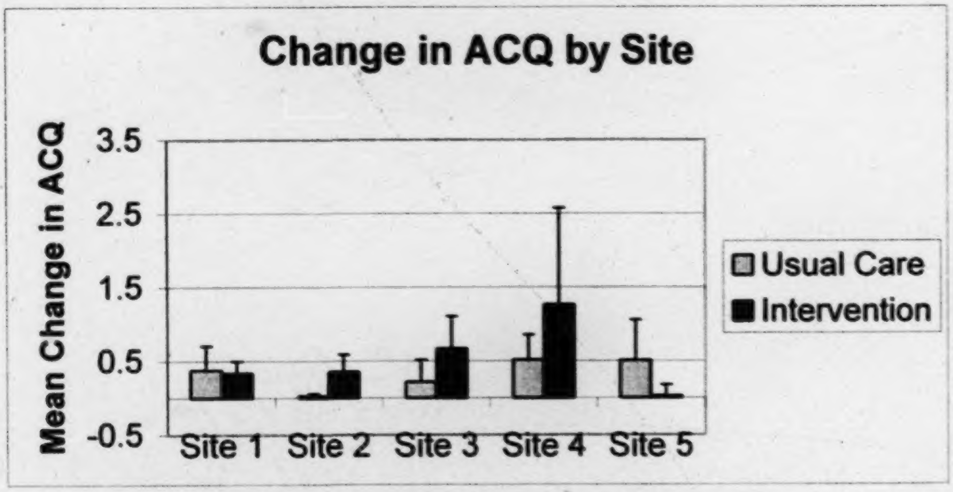

Figure 3.7: Mean change in ACQ (+ SE of mean) by site

From Figure 3.7, it is apparent that there may be differences in change in ACQ based on site. There are wide variations in change scores between sites. Intervention patients at Site 4 show the most improvement in ACQ scores. Site 5 shows more improvement in asthma control in the UC group compared to the intervention. The mean change in ACQ between sites was tested for heterogeneity and the results were not significant (p=0.14).

These potential site differences were tested for significance (Table 3.10).

Table 3.10: Comparison of change in ACQ stratified by site

| Variable | Usual Care Mean change in ACQ (SE) | Intervention Mean change in ACQ (SE) | Difference between groups |
|---|---|---|---|
| Site 1 | 0.38 (0.33) | 0.34 (0.16) | t = 0.117, 29 df, p=0.91 |
| Site 2 | 0.03 (0.03) | 0.36 (0.23) | t = -1.31, 9 df, p=0.22 |
| Site 3 | 0.22 (0.30) | 0.67 (0.44) | t = -0.86, 10 df, p=0.41 |
| Site 4 | 0.52 (0.34) | 1.27 (1.31) | t = -0.552, 4 df, p=0.61 |
| Site 5 | 0.51 (0.55) | 0.03 (0.15) | t = 0.847, 8 df, p=0.42 |

There were no statistically significant differences in site. Both Site 1 and Site 5 had greater change in ACQ in UC group patients. Site 4 had the largest difference in change in ACQ between UC and intervention. The SE is quite large for some of the values due to the small number of patients randomized within each site.

#### *3.3.1.4 Regression model for change in ACQ*

In the regression model, the change in ACQ was initially adjusted for gender, age and site as specified *a priori*. Given that there were no significant differences found in the descriptive analyses, it was not anticipated that these factors would make a significant contribution to the regression model.

Table 3.11: Linear regression model for change in ACQ

| **Variable** | **Significance of change in F-statistic** | **Unstandardized Beta-coefficients (SE)** | **Overall model significance** |
|---|---|---|---|
| Treatment group | N/A | 0.100 (0.226) | F=0.196, df 1,68 |
| | (comparison model) | | p=0.66 |
| Treatment group | F=0.111, df 1, 65 | 0.137 (0.236) | F=0.200, df 2, 65 |
| Age | p=0.74 | 0.004 (0.011) | p=0.82 |
| Treatment group | F=0.199, df 1, 65 | 0.122 (0.233) | F=0.245, df, 2,65 |
| Gender | p=0.66 | 0.104 (0.234) | p=0.78 |
| Treatment group | F=0.584, df 4, 64 | 0.106 (0.229) | F=0.505, df 5, 64 |
| Site 2 | p=0.68 | -0.156 (0.335) | p=0.77 |
| Site 3 | | 0.087 (0.325) | |
| Site 4 | | 0.538 (0.426) | |
| Site 5 | | -0.088 (0.347) | |
| Treatment group | F=0.392, df 6, 60 | 0.127 (0.241) | F=0.376, df 7, 60 |
| Age | p=0.88 | 0.002 (0.012) | p=0.91 |
| Gender | | 0.144 (0.246) | |
| Site 2 | | -0.079 (0.377) | |
| Site 3 | | 0.101 (0.337) | |
| Site 4 | | 0.574 (0.443) | |
| Site 5 | | -0.037 (0.373) | |

In Table 3.11 it is apparent that the change in ACQ was still not significant, even after controlling for age, gender and site. There were no differences in each of these factors alone (Tables 3.8, 3.9, 3.10) and as a group they do not contribute to the prediction of change in ACQ. As none of these covariates contribute significantly to the model, their interaction terms were not analyzed.

The model was also adjusted for factors which, at baseline, were significantly different between the 2 groups (Table 3.12). These factors included self-reported unscheduled physician visits in the 6-months prior to the baseline visit, previous pulmonary function testing, inhaler technique and use of a PEF meter (Table 3.3).

Table 3.12: Adjusted linear regression model for factors significantly different at baseline

| **Variable** | **Significance of change in F-statistic** | **Unstandardized Beta-coefficients (SE)** | **Overall model significance** |
|---|---|---|---|
| Treatment group | (comparison model) | 0.100 (0.226) | F=0.196, df 1, 68<br>p=0.66 |
| Unscheduled physician visits in previous 6-months | F=0.225, df 1, 67<br>p=0.64 | -0.114 (0.239) | F=0.209, df 2, 67<br>p=0.81 |
| Previous pulmonary function testing | F=0.659, df 1, 67<br>p=0.42 | 0.189 (0.233) | F=0.427, df 2, 67<br>p=0.65 |
| Inhaler technique | F=4.296, df 1, 67<br>**p=0.04** | 0.562 (0.271) | F=2.251, df 2, 67<br>p=0.11 |
| PEF monitoring | F=0.110, df 1, 67<br>p=0.74 | -0.095 (0.286) | F=0.151, df 2, 67<br>p=0.86 |

Inhaler technique significantly contributes to the linear regression model with treatment group (p=0.04), however the overall model was still not significant. This factor will therefore be controlled for in further analyses. The other factors, which were significantly different at baseline, had no significant effect on the prediction of change in ACQ.

In both unadjusted and adjusted analysis, there is no significant difference between UC and intervention in terms of change in ACQ.

## 3.4 Secondary Endpoints

### 3.4.1 Inhaled Corticosteroid Use

As a secondary endpoint assessing the effectiveness of the pharmacists recommendations inhaled corticosteroid use in UC and intervention were analyzed. At baseline, over 25% of patients were not on inhaled corticosteroids (Table 3.6).

Table 3.13: Inhaled corticosteroid use at baseline and 6-months

| | **Usual Care (n=34) N (%)*** | **Intervention (n=36) N (%)** | **Difference between groups** |
|---|---|---|---|
| Baseline | 26 (76.4) | 25 (69.4) | NS |
| 6-months | 28 (82.3) | 30 (83.3) | NS |

There was no difference between the 2 groups regarding inhaled corticosteroid use at 6-months (OR = 0.720, 95% CI 0.271, 1.917) (Table 3.13). When a logistic regression model was used, controlling for inhaler technique and inhaled corticosteroid use at baseline, there was still no significant difference between UC and intervention (OR = 0.68, 95% CI 0.22, 2.06). The only factor significantly predictive of being on an inhaled corticosteroid at 6 months was being on an inhaled corticosteroid at baseline (OR = 5.58, 95% CI 1.76, 17.63).

### 3.4.2 Forced Expiratory Volume in 1 Second ($FEV_1$)

Change in $FEV_1$ from baseline to 6-months was calculated (as percent predicted) and compared between UC and intervention (Table 3.14). An increase in $FEV_1$ indicates improvement in lung function and a decrease in $FEV_1$ indicates worsening of lung function.

Table 3.14: Mean change in $FEV_1$ from baseline to 6-months

| | **Usual Care Mean change in $FEV_1$ (SE)** | **Intervention Mean change in $FEV_1$ (SE)** | **Difference between groups** |
|---|---|---|---|
| Change in $FEV_1$ (percent predicted) from baseline to 6-months | 2.96 (1.46) | 0.55 (1.28) | t = 1.244, 68 df<br>p=0.22 |

There was no statistically significant difference in change in $FEV_1$ as compared between intervention and UC. The mean change in both groups was minimal as displayed in Figure 3.8.

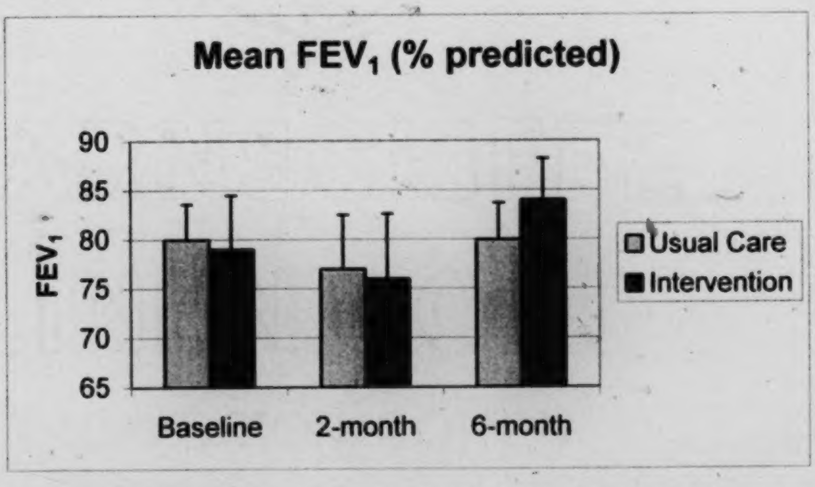

Figure 3.8: Mean $FEV_1$ (+SE) at baseline, 2-months and 6-months

To determine if there were any differences at each visit, the mean $FEV_1$ was compared at baseline, 2-months and 6-months (Table 3.15).

Table 3.15: Comparison of mean $FEV_1$ at baseline, 2-months and 6-months

| **Follow-up Visit** | **Usual Care Mean $FEV_1$ (SE)** | **Intervention Mean $FEV_1$ (SE)** | **Difference between groups** |
|---|---|---|---|
| Baseline | 80 (3.6) | 79 (5.5) | t = 0.160, 50 df<br>p=0.87 |
| 2-month | 77 (5.5) | 76 (6.6) | t = -0.008, 43 df<br>p=0.99 |
| 6-month | 80 (3.7) | 84 (2.2) | t = -0.771, 39 df<br>p=0.45 |

The mean $FEV_1$ at 2-months was lower (worsening of $FEV_1$) than at baseline in both UC and intervention, but not statistically significant. There was no statistically significant difference in $FEV_1$ at any follow-up visit.

In a linear regression model controlling for inhaler technique, treatment group was still not predictive of change in $FEV_1$ (F=0.919, df 2, 67, p=0.40).

### 3.4.3 Courses of Oral Steroids

To analyze the courses of oral steroids patients received during the study, the normality of the distribution was first assessed (Figures 3.9 and 3.10).

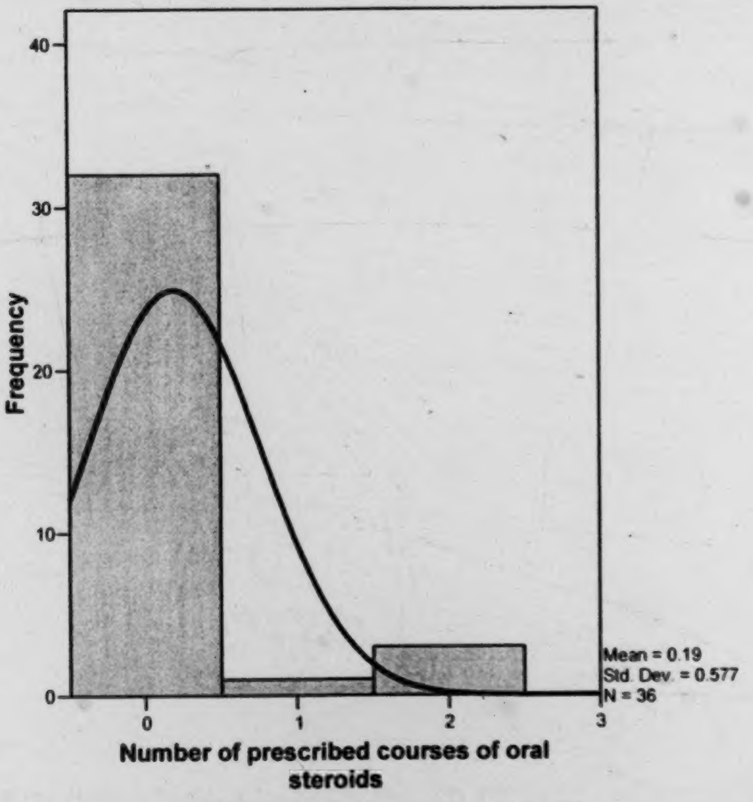

Figure 3.9: Distribution of number of courses of oral steroids prescribed over 6-months in intervention patients

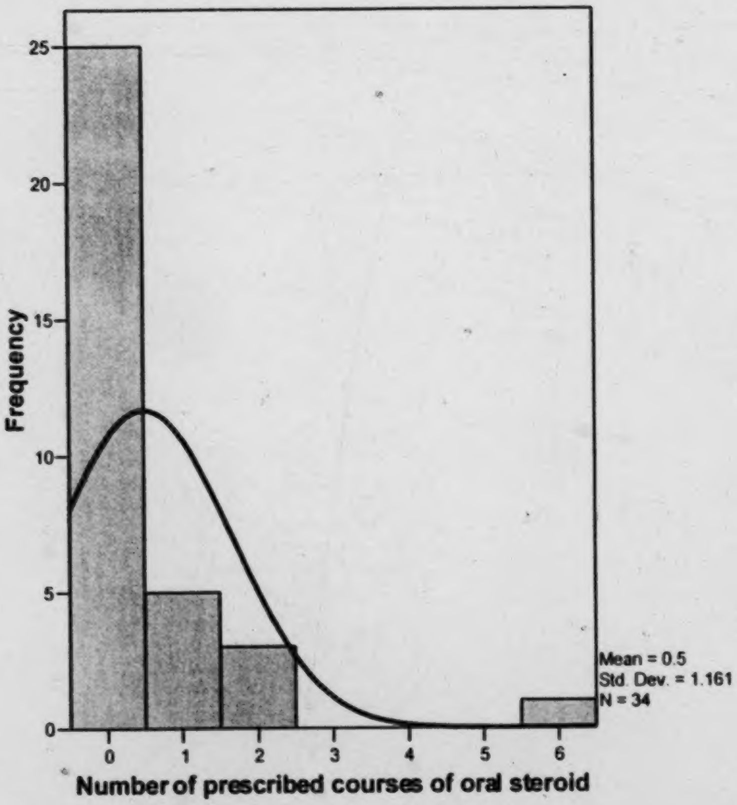

Figure 3.10: Distribution of number of courses of oral steroids prescribed over 6-months in usual care patients

As the distribution of number of courses was not normal, data was dichotomized in to whether or not patients had received any course of oral steroid over the study period (Table 3.16). Courses of oral steroids were initially compared using a Chi-square test (dichotomized outcome) and then modeled with logistic regression.

Table 3.16: 2x2 table of number of patients who received a short-course of oral steroids during study period

| | Received course of oral steroid | | Total (%) |
|---|---|---|---|
| | No (%) | Yes (%) | |
| **Usual Care** | 25 (73.5) | 9 (26.5) | 34 (48.6) |
| **Intervention** | 32 (88.9) | 4 (11.1) | 36 (51.4) |
| **Total** | 57 (81.4) | 13 (18.6) | 70 (100) |

The number of courses of oral steroids prescribed to UC was not significantly different from the number of courses prescribed to intervention (OR = 0.35, 95% CI 0.10, 1.26).

Oral steroid courses were then analyzed in a logistic regression model, as displayed in Table 3.17, adjusting for treatment group and previous courses of oral steroids.

Table 3.17: Logistic regression model for courses of oral steroids

| Variables | Odds Ratio (95% CI) | Significance |
|---|---|---|
| Intervention | 0.28 (0.07, 1.12) | p=0.08 |
| Previous course of oral steroids | 7.89 (1.97, 31.52) | p=0.003 |

From the logistic regression model controlling for previous courses of oral steroid, treatment group was still not predictive of whether a patient would receive an oral steroid, however it approached statistical significance (p=0.08). Intervention patients were less likely to have a course of oral steroids prescribed during the study.

Previous courses of oral steroids significantly predicted whether a patient was going to receive a course of oral steroid during the study. Patients with a previous course of oral steroid were 8 times more likely to receive a course of oral steroid during the study.

### 3.4.4 ED visits and Hospitalizations

In Figures 3.11 and 3.12, the distribution of the number of ED visits or hospitalizations was assessed to determine if it was normally distributed.

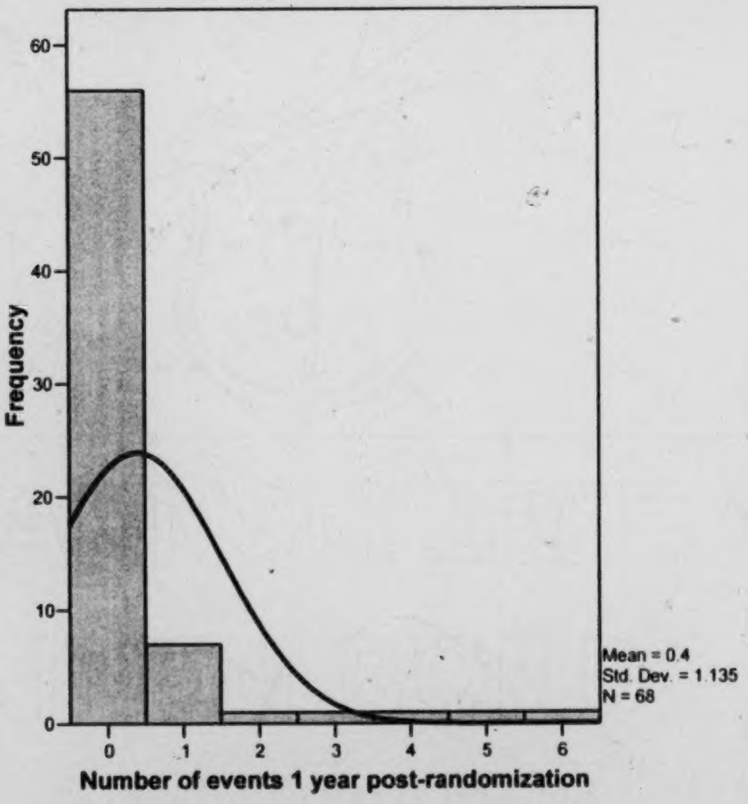

Figure 3.11: Number of ED visits / hospitalizations up to 1-year post-randomization in intervention patients

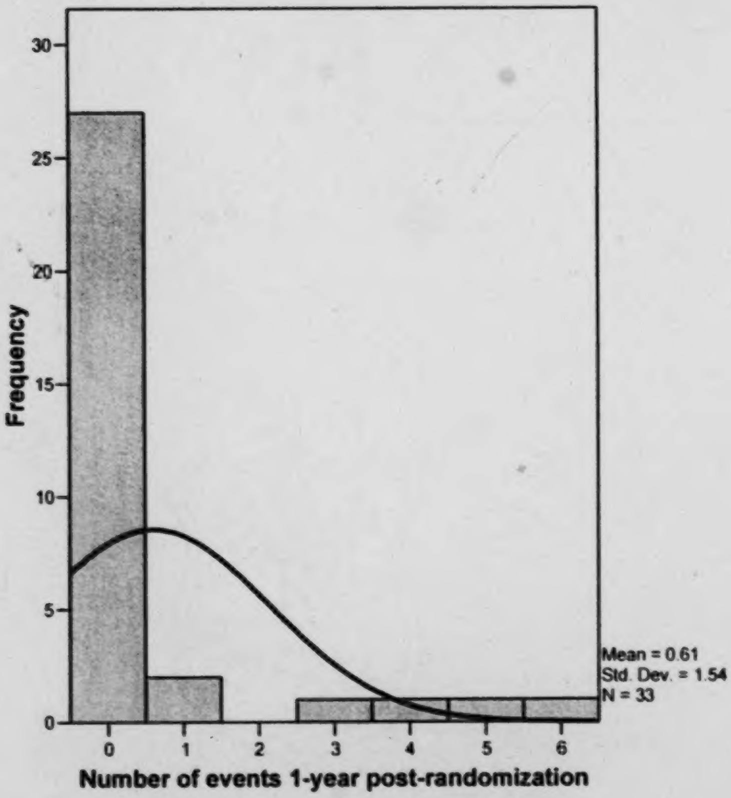

Figure 3.12: Number of ED visits / hospitalizations up to 1-year post-randomization in usual care patients

The distribution of number of ED visits /hospitalizations is not normal, therefore to compare ED visits and hospitalizations the data was dichotomized into any ED visit / hospitalization or no ED visit / hospitalization (Table 3.18).

Table 3.18: 2x2 table of ED visits / hospitalizations post-randomization

| | Hospitalization / ED visit | | Total (%) |
|---|---|---|---|
| | No (%) | Yes (%) | |
| **Usual Care** | 28 (82.4) | 6 (17.6) | 34 (48.6) |
| **Intervention** | 30 (83.3) | 6 (16.7) | 36 (51.4) |
| **Total** | 58 (82.9) | 12 (17.1) | 70 (100) |

The number of hospitalizations / ED visits was not significantly different between UC and intervention (OR 0.93, 95% CI 0.27, 3.24).

The ED visits and hospitalizations was then analyzed in a logistic regression model controlling for ED visit / hospitalization prior to enrollment in the study (Table 3.19).

Table 3.19: Logistic regression model for ED visits / hospitalizations

| Variable | Odds Ratio (95% CI) | Significance |
|---|---|---|
| Intervention | 1.08 (0.30, 3.93) | p=0.91 |
| Previous ED visit or hospitalization | 3.47 (0.90, 13.39) | p=0.07 |

Neither treatment group nor previous event were predictive of an outcome of ED visit / hospitalization.

## 3.5 Education Provided

### 3.5.1 Pharmacist Provided Education

The pharmacists had the greatest opportunity to provide education to the intervention patients at the 5 scheduled follow-up visits. The most commonly provided education was regarding medications followed by control of environment factors, as listed in Table 3.20.

Table 3.20: Pharmacist-provided education throughout the study (n=36)

| Education | Baseline<br>N (%) | 2-week<br>N (%) | 1-month<br>N (%) | 2-month<br>N (%) | 4-month<br>N (%) | 6-month<br>N (%) |
|---|---|---|---|---|---|---|
| Medications | 31<br>(86.1) | 20<br>(55.6) | 24<br>(66.7) | 20<br>(55.6) | 18<br>(50.0) | 23<br>(63.9) |
| Written Action Plan | 7<br>(19.4) | 10<br>(27.8) | 15<br>(41.7) | 14<br>(38.9) | 12<br>(33.3) | 11<br>(30.6) |
| Environmental Factors | 32<br>(88.9) | 17<br>(47.2) | 22<br>(61.1) | 20<br>(55.6) | 17<br>(47.2) | 21<br>(58.3) |
| Inhaler Use | 14<br>(38.9) | 15<br>(41.7) | 20<br>(55.6) | 13<br>(36.1) | 10<br>(27.8) | 15<br>(41.7) |
| PEF Monitoring | 14<br>(38.9) | 11<br>(30.6) | 19<br>(52.8) | 16<br>(44.4) | 11<br>(30.6) | 10<br>(27.8) |
| Smoking Cessation | 12<br>(33.3) | 6<br>(16.7) | 6<br>(16.7) | 5<br>(13.9) | 7<br>(19.4) | 7<br>(19.4) |

Education on WAP was the highest at the 1-month visit, with about 40% of patients receiving education. At all visits, less than 50% of the patients received WAP education. The goal was to have 100% education on WAP at each visit.

### 3.5.2 RT-Provided Education

The RT visits were primarily for the measurement of pulmonary function. The RT also had a role in reinforcement of education provided by the pharmacist. The RT focused his education sessions on inhaler technique and medications.

Table 3.21: RT-provided education throughout the study (n=36)

| Education | Baseline<br>N (%) | 2-month<br>N (%) | 6-month<br>N (%) |
|---|---|---|---|
| Medications | 25 (69.4) | 21 (58.3) | 20 (55.6) |
| Written Action Plan | 8 (22.2) | 8 (22.2) | 8 (22.2) |
| Environmental Factors | 24 (66.7) | 21 (58.3) | 19 (52.8) |
| Inhaler Use | 25 (69.4) | 21 (58.3) | 18 (50.0) |
| Peak Flow Monitoring | 3 (8.3) | 5 (13.9) | 1 (2.8) |
| Smoking Cessation | 9 (25.0) | 4 (11.1) | 2 (5.6) |

As shown in Table 3.21, at each visit, less than 25% of the intervention patients received education on WAP from the RT. The goal was to have 100% education on WAP at each visit.

### 3.6 Recommendations Made

Pharmacists were encouraged to make recommendations to the patient or physician based on their assessment at any visit, for participants randomized to intervention. The types of recommendations that could be made included adding an inhaled corticosteroid, changing current inhaled corticosteroid dose, adding another asthma medication to current therapy, changing short-acting beta-2 agonist dose, or other recommendations (e.g., stopping medications that may induce asthma symptoms).

Table 3.22: Recommendations made by pharmacist (n=36)

| **Recommendations** | **Baseline**<br>**N (%)** | **2-wk**<br>**N (%)** | **1-mo**<br>**N (%)** | **2-mo**<br>**N (%)** | **4-mo**<br>**N (%)** | **6-mo**<br>**N (%)** |
|---|---|---|---|---|---|---|
| Add inhaled steroid | 6<br>(16.7) | 6<br>(16.7) | 1<br>(2.8) | 2<br>(5.6) | 0<br>(0) | 1<br>(2.8) |
| Change steroid dose | 0<br>(0) | 0<br>(0) | 4<br>(11.1) | 1<br>(2.8) | 0<br>(0) | 0<br>(0) |
| Add other medication | 1<br>(2.8) | 1<br>(2.8) | 2<br>(5.6) | 3<br>(8.3) | 1<br>(2.8) | 1<br>(2.8) |
| Change short-acting beta-2 agonist | 0<br>(0) | 0<br>(0) | 0<br>(0) | 0<br>(0) | 0<br>(0) | 0<br>(0) |
| Other recommendations | 8<br>(22.2) | 8<br>(22.2) | 5<br>(13.9) | 5<br>(13.9) | 3<br>(8.3) | 1<br>(2.8) |
| No recommendations | 21<br>(58.3) | 21<br>(58.3) | 24<br>(66.7) | 25<br>(69.4) | 32<br>(88.9) | 33<br>(91.7) |

From Table 3.23, the most common type of recommendation was "other" recommendations, and included recommendations to follow-up with primary physician, addition of oral steroid, peak flow monitoring, and compliance aids. The most common medication-related recommendation was addition of an inhaled corticosteroid, and this occurred 16 times over the course of the study.

In over 50% of patients no recommendation was made at all visits.

## 3.7 Follow-up Visits

### 3.7.1 Pharmacist Follow-up Visits

The patients in intervention group had a total of 5 scheduled follow-up visits over the course of the study. The 2-week and 4-month visits were a telephone follow-up, to limit the number of times patients were required to come into the pharmacy. In contrast, UC patients only at 2 follow-up visits, both of which were to be conducted in-person.

Table 3.23: Completed follow-up with the pharmacist

| **Visit** | **Usual Care (n=34) N (%)** | **Intervention (n=36) N (%)** | **Difference between Groups** |
|---|---|---|---|
| 2-week | N/A | 21 (58.3) | N/A |
| 1-month | N/A | 23 (63.9) | N/A |
| 2-month | 26 (74.3) | 23 (63.9) | $X^2$=0.897, 1df<br>p=0.34 |
| 4-month | N/A | 20 (55.6) | N/A |
| 6-month | 28 (80.0) | 24 (66.7) | $X^2$=1.610, 1 df<br>p=0.21 |

Patients in the intervention group had poorer visit compliance compared to patients in UC, although it was not statistically significant at the 2 and 6 month visits (Table 3.24). Only two-thirds of patients in intervention completed their 6-month follow-up visit with the pharmacist. There was never more than 67% visit completion at any intervention follow-up over the entire study.

### 3.7.2 RT Follow-up Visits

Patients in both UC and intervention had the same number of required follow-up visits to complete with the RT, for measurement of lung function and administration of the ACQ. Intervention patients also received some education from the RT at these visits.

Table 3.24: Completion of follow-up with the RT

| **Visit** | **Usual Care (n=34) N (%)** | **Intervention (n=36) N (%)** | **Difference between groups** |
|---|---|---|---|
| Baseline | 28 (80.0) | 25 (69.4) | $X^2$=1.775, 1 df p=0.18 |
| 2-month | 25 (71.4) | 23 (63.9) | $X^2$=0.754, 1 df p=0.39 |
| 6-month | 22 (62.9) | 24 (66.7) | $X^2$=0.030, 1 df p=0.86 |

In UC, the patients completed their RT visits 71.4% of the time (Table 3.25). Intervention patients completed 66.7% of their RT visits during the study.

Overall, less than two-thirds of the study participants completed their 6-month follow-up and ACQ measurement with the RT, which was part of the primary outcome measurement.

Table 3.25: Number of patients completing 6-month RT and pharmacist follow-ups

| **Completion of 6-months visits** | **Number of Patients (n=70) N (%)** |
|---|---|
| Neither 6-month visit complete | 12 (17.1) |
| Either pharmacist or RT 6-month visit complete | 18 (25.7) |
| Completed both pharmacist and RT 6-month visit | 40 (57.1) |

Only 57% of the study patients completed both portions of the 6-month follow-up (Table 3.26). Almost 20% of the study population completed neither the RT nor the pharmacist portion of the final follow-up visit.

## 3.8 Additional Analyses

### 3.8.1 Analysis of Patients with Complete Follow-up

An analysis was conducted including only patients who completed their 6-month RT visit, as this was the visit which included measurement of the ACQ. This is shown below in Table 3.27.

Table 3.26: Comparison of change in ACQ from baseline to 6-months in patients who completed 6-month RT visit

| | **Usual Care Mean change in ACQ (SE) (n=22)** | **Intervention Mean change in ACQ (SE) (n=24)** | **Difference between groups** |
|---|---|---|---|
| Change in ACQ from baseline to 6-months | 0.41 (0.25) | 0.64 (0.20) | t = -0.719, 44 df<br>p=0.48 |

There was no difference in change in ACQ between usual care and intervention. In both groups the mean change in ACQ was higher than in the intention-to-treat analysis.

As there were 2 components to the 6-month follow-up, an analysis was conducted to compare change in ACQ in patients who completed both the RT and pharmacist portions of the 6-month follow-up, as shown in Table 3.28.

Table 3.27: Comparison of change in ACQ from baseline to 6-months in patients who completed both 6-month RT and pharmacist follow-up

| | **Usual Care Mean change in ACQ (SE) (n=19)** | **Intervention Mean change in ACQ (SE) (n=21)** | **Difference between groups** |
|---|---|---|---|
| Change in ACQ from baseline to 6-months | 0.30 (0.26) | 0.68 (0.22) | t = -1.12, 38 df<br>p=0.27 |

The change in ACQ from baseline to 6-months is not significantly different between UC and intervention in patients who completed both the RT and pharmacist 6-month follow-up.

### 3.8.2 Analysis of Patients with Written Action Plans

Development of a WAP for every intervention patient was an integral part of the intervention. Although the WAP was the emphasis of the intervention, only 75% of patients received a WAP over the course of the study. The pharmacists educated 64% (n=23) of patients about WAPs over the course of the study, and the RT educated 42% (n=15) of patients over the course of the study (Tables 3.20 and 3.21).

To determine if WAP education had an effect on outcome, we compared change in ACQ in intervention patients who had WAP education to intervention patients who did not receive WAP education.

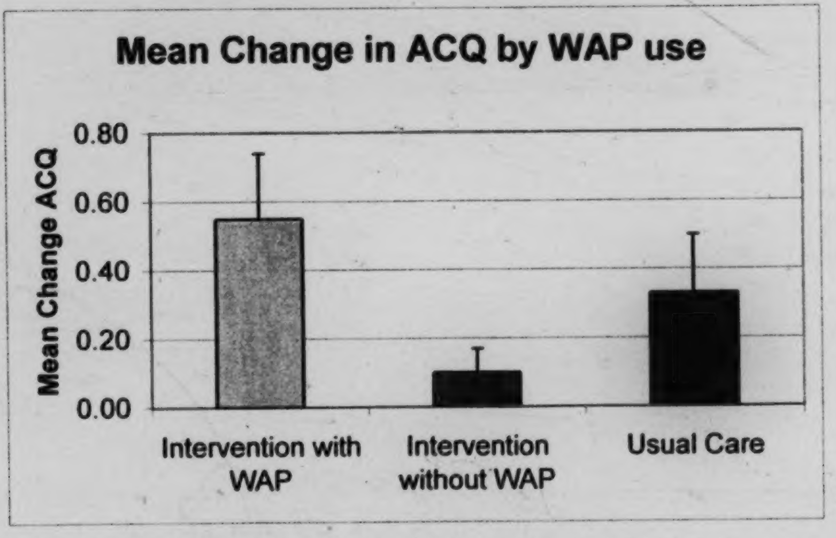

Figure 3.13: Comparison of mean change in ACQ (+ SE of mean) in patients with and without a WAP

Although the numbers are small, it appears in Figure 3.13 that intervention patients with a WAP had more change in ACQ than intervention patients without a WAP. Using a one-sample t-test, comparing intervention patients with and without a WAP, there was a significantly different change in ACQ (t=10.25, 35 df, p<0.001). When the three groups were compared (intervention patients with WAP, intervention patients without a WAP and usual care), there was no significant difference across the groups.

WAP was included in a regression model to evaluate whether it made a difference in change in ACQ (Table 3.22).

Table 3.28: Linear regression model controlling for written action plans

| Variable | Significance of change in F-statistic | | Overall model significance |
|---|---|---|---|
| Treatment group | (comparison model) | 0.221 (0.228) | F=2.251, df 2, 67 |
| Inhaler technique | | 0.562 (0.271) | p=0.11 |
| Written action plan | F=1.088, df 1, 66 | 0.372 (0.357) | F=1.87, df 3, 66 |
| | p=0.30 | | p=0.14 |

After controlling for WAP, treatment group was still not predictive of change in ACQ.

### 3.8.3 Analysis of Primary Outcome as a Before-After Design

Many pharmacy practice studies employ a before-after design, as there are issues involved with having a control group, such as contamination and pharmacists' desire to provide an intervention to all of their patients (107;108). If we had used a before-after design with BREATHE, and analyzed the results from the intervention group only using a paired t-test, the change in ACQ from baseline to 6-months is statistically significant (t=2.94, 35df, p=0.006).

## 3.9 Summary of Results

In summary, there was no difference found between the intervention and usual care groups with regards to asthma control (primary endpoint). There were also no statistically significant differences in lung function, inhaled corticosteroid use and ED visits/hospitalizations (secondary endpoints). The secondary endpoint of courses of oral steroids approached statistical significance (p=0.08), favouring intervention. In a post-hoc analysis, it appears that intervention patients who did receive a WAP plan improved significantly more than intervention patients who did not. Overall, patient follow-up and application of the intervention (as measured by WAP education) by investigators was poor.

# Chapter 4 Discussion and Conclusions

Asthma affects approximately 10% of Canadians and is associated with high health-care utilization. Although mortality attributable to asthma is low, asthma-related morbidity occurs frequently, which adversely affects quality of life and leads to increased health-care costs. Factors associated with lower health-care utilization include appropriate medication use and education including a WAP (109;110).

Previous research has shown there are a number of care-gaps associated with asthma management (58;111;112). These include, but are not limited to, low use of inhaled corticosteroid, low use of WAP and overestimation of asthma control (58;63;113-119). The care-gaps provide us with targeted areas for intervention to enhance asthma care in patients.

Management of asthma requires involvement of the patient and their health-care providers, including their primary-care physician, RT and community pharmacist. Patients in rural communities have less opportunity to have follow-up with specialists; therefore the majority of their care is managed by primary health-care providers. By directing interventions at identified care gaps and involving key health-care providers, asthma control can be improved.

The BREATHE study was a randomized, controlled trial of a community-based asthma intervention. The primary objective of this study was to determine if a community-based asthma management program could improve asthma control in "high-risk" asthma patients. The intervention included medication assessment, education (with a focus on WAP development) and referral to physician and RT. The study was initiated at the community pharmacy level; other primary-health providers were involved after enrollment.

The results were consistent for all measured endpoints; there was no detectable difference between the intervention group and the usual care group. Supplementary analysis was conducted to elucidate why no differences were found, with some promising results. Even though the results may be considered "negative", the study provides useful information regarding the design and implementation of rural, community-based, pharmacist-initiated interventions.

### 4.1 Comparison of BREATHE and A.S.T.H.M.A. Study Patients

The BREATHE study population appears to be similar to the general Alberta population and other asthma study populations, therefore suggesting the results are generalizable. Approximately 53% of the BREATHE sample was female, which compares to the number of female asthmatics in the ASTHMA study. The numbers of current smokers is comparable between ASTHMA and BREATHE patients (58). The education level of BREATHE study participants is similar to the provincial average (120).

In terms of baseline medications, the documented inhaled steroid use was higher in the BREATHE study as compared to the ASTHMA sample (75% compared to 68%). The most noticeable difference in the 2 populations in terms of medication use was the number of patients on long-acting beta-agonists. In BREATHE over 30% of patients were on a long-acting beta-agonists, whereas it was reported in less than 10% of ASTHMA study patients. This difference may be reflective of differences in severity of asthma, as BREATHE attempted to target a higher risk group. The difference in long-acting beta-agonist use may also be due to the when the studies were conducted. ASTHMA data collection occurred between 1996 and 2001, whereas BREATHE started enrollment near the end of 2002. In the 1999 Canadian Asthma Consensus Guidelines, the choice for add-on therapy included both long-acting beta-agonists and leukotriene receptor antagonists (32). Recent literature has shown the benefit of long-acting beta-agonists as add-on therapy to inhaled corticosteroids (121-123). In the most recent update of the Canadian Asthma Consensus Guidelines, long-acting beta-agonists are supported as the first-line add-on therapy (33). The British Thoracic Society guidelines also recommend long-acting beta-agonists as first-line add-on therapy (35). Recent literature and changes in guidelines may be the explanation for the difference in long-acting beta-agonist use between ASTHMA and BREATHE, as BREATHE is more reflective of current use of long-acting beta-agonists.

Self-monitoring is difficult to compare between ASTHMA and BREATHE as the data was collected differently. Approximately 10% of the sample in ASTHMA received some documented education regarding home PEF monitoring; in contrast, 21% of patients reported actively using PEF meters for self-monitoring in BREATHE.

The number of asthma-related ED visits and hospitalizations prior to randomization are comparable to the reported population average of 18-28% per year (2). A total of 20% of BREATHE patients enrolled had at least 1 event the year prior to randomization. This is only reflective of events that occurred in Hinton or Edson, therefore may be an underestimate.

A difference between BREATHE and ASTHMA is seen with regards to previous pulmonary function testing (PFT). In ASTHMA 30% of the adults reported having previous PFT whereas over 50% of BREATHE patients reported having prior PFT. This may reflect access to care, as Hinton and Edson both have facilities available to conduct PFT and there is not a waiting list to see the RT for PFT. Alternatively, as the BREATHE study participants were high-risk, they may be more likely to have had previous PFT.

The baseline demographics help us to determine whether the BREATHE study population is a sample reflective of asthma patients. From the data we have available, it appears that BREATHE patients are comparable to other asthma patients, making the results generalizable to other asthma patients. The differences (increasing inhaled corticosteroid use, higher reporting of prior PFT, increased PEF meter use, increased use of long-acting beta-2 agonists), may be indicative of the higher-risk population in BREATHE.

## 4.2 Primary Outcome

The primary outcome measure was the change in ACQ from baseline to 6-months. The difference in the change in ACQ between UC and intervention groups was not significant. Even after controlling for a number of variables (including age, gender, site, unscheduled physician visits, previous PFTs, adequate inhaler technique and use of PEF meter) there was still no significant difference between the two groups. The UC group had a 0.33 change in ACQ and the intervention group had a 0.43 change over 6-months.

There are a number of reasons that can help explain why no difference was found between UC and intervention in terms of asthma control.

### 4.2.1 Contamination of Usual Care Group

There may have been contamination of the usual care group as all the caregivers involved in the study were unblinded. The intervention, or components of it, could have been administered to the usual care group. Cointerventions can occur unequally between the study groups, which introduces bias. These issues were identified as potential limitations before study initiation. The benefits of the rigorous study design, most notably a higher causal inference, outweighed the risk of contamination. This limitation cannot be controlled for with statistical analysis.

Contamination can only be controlled via study design (internal validity), primarily by blinding the investigators, patients and outcome assessors. BREATHE was not blinded for logistical reasons. Unblinded trials may more accurately reflect clinical practice and the goal of BREATHE was to emulate "real-world" practice (124). The effectiveness of this program was being tested, as opposed to the efficacy.

Contamination could have been introduced by the pharmacists, the RT or the primary-care physicians, all of who were involved in the implementation of the study.

The pharmacists could have contaminated the UC group by administering parts of the educational components to the UC patients. For example, at Site 1, two of the pharmacists were certified asthma educators. These pharmacists provided a high-level of asthma care to their patients prior to the study and this was likely continued after study initiation (as "usual care"). As seen in the results for the patients enrolled from site 1, the change in ACQ is almost exactly the same in UC and intervention group (Figure 3.7). The alternative to randomization by patient would have been randomization by site, to help reduce contamination by the pharmacist investigators. The method has been used in other health-services research and pharmacist-intervention studies (125;126). However, there are also concerns with randomization by site. Firstly, capturing and controlling for differences in demographics and socioeconomic status would have been more difficult with randomization by site. Secondly, from initial meetings, it was apparent that for the pharmacists to commit to involvement, they wanted to be able to have the opportunity to administer the intervention. Finally, as there were only 5 sites involved in the study, cluster randomization would have been difficult. There were major differences in the number of participants recruited by site (Table 3.1) and this would have affected the number of patients in each study group potentially causing unbalanced numbers of UC and intervention patients. Moreover, sample sizes for cluster randomization require inflation (127). The sample size is calculated based on the primary outcome measure and then adjusted with an inflation factor. The inflation factor takes into account the number of clusters, size of each cluster, between cluster variance and within cluster variance. Inflation factors generally range from 1.5 and higher, therefore conservatively, 50% more patients may have been required to adjust for cluster randomization to have adequate statistical power (127). As there was difficulty in recruiting patients in BREATHE, it would have been an even greater challenge with the larger sample size requirement for cluster randomization. Randomization by site would still not have controlled for contamination by the physicians or RT.

It was apparent during the first few months of recruitment that the RT was not keeping the intervention group and UC groups separate. For example, we discovered that he was often using incorrect case report forms. In the case of using intervention case report forms for UC, the intervention case report forms included prompts for the educational components of the intervention. This required constant monitoring by the project team to ensure contamination was minimized, however, this could not be fully controlled.

The physicians were another source of possible contamination. It is possible that merely the identification of patients by the pharmacist and subsequent PFT of all patients was enough of an impetus to have the physicians make appropriate changes to patient's asthma management. Physicians were sent faxes from the pharmacists regarding only the intervention patients, however, they would have been notified by the RT regarding PFT results in any patient, especially if there was a concern. This would be consistent in UC and intervention, therefore contributing to the neutral effect of the intervention. Also, we consulted with all family physicians prior to starting the study, presenting the objectives, design, and procedures of the study. This may have caused a Hawthorne effect in usual care patients (128).

### 4.2.2 Application ("Dose") of Intervention

All sites did not uniformly apply the intervention. Based upon case report forms received, follow-up was poor, few management recommendations were made, and 25% of patients in intervention never received a WAP.

The follow-up completed at each site varied, indicating a difference in the strength of how the intervention was applied. Only 30% of patients at site 5 completed their 6-month follow-up with the pharmacist and 27% of patients at site 2 completed their 6-month RT follow-up. The low rate of follow-up would lead us to believe there was minimal intervention applied at these sites.

The differences between site and change in ACQ are hard to interpret, as there are large differences in the number of patients randomized. Intervention patients at Site 5 had no change at all in the ACQ, whereas usual care patients had an improvement in asthma control. This suggests that the intervention was not being applied to all intervention patients. The site which had the best follow-up (Site 4), also showed the greatest change in ACQ.

The main recommendations made over the study include "other" recommendations and adding an inhaled corticosteroid. At the baseline and 2-week visit, 56% of patients had no recommendations made. From research we have conducted with a previous pharmacist-intervention study, early recommendations have the most impact on the outcomes (129). The baseline and first follow-up visits are vital to achieving the desired outcome. Given that over half the intervention patients had no recommendations made, this may have contributed to the neutral findings of our study.

From the secondary analyses, the patients in intervention who did receive a WAP did significantly better than those who did not. The WAP was an integral part of the intervention and all intervention patients should have received some education regarding it. Approximately 22% of intervention patients were on a combination inhaled corticosteroid and long-acting beta-2 agonist product. These combination products can limit the usefulness of WAP as not all combination products can be adjusted incrementally for an increase in symptoms, as would be dictated by a WAP. The low rate of WAP usage may have been affected by the high rate of combination products used by the study population. Moreover during pharmacist training, it was stressed that the standard doubling of dose approach to inhaled corticosteroids should be applied in response to increasing symptoms. Recent data suggest that this approach may not be effective and a quadrupling of inhaled steroid may be required for exacerbations (130;131).

It is apparent from the analysis that the "dose" of the intervention was quite low, especially at Sites 2 and 5. Poor follow-up, as well as the difference in administration of the intervention between sites, as evidenced by low number of recommendations and WAP education, contributed to the lack of response in the intervention group.

### 4.2.3 Losses to Follow-up

Although there were enough patients for 90% power (section 4.2.4), there were still a number of losses to follow-up. Only 40 patients completed both components of the 6-month follow-up. The concern is that the patients who did not complete follow-up may be systematically different from the patients who did, therefore leading to bias.

Approximately one-third of patients did not complete their final 6-month visit. As specified by the protocol, if there was no ACQ measurement available, the last value available was carried forward. This method assumes no change and therefore would have an effect on the overall reported change in ACQ, favouring the null hypothesis.

Patients lost to follow-up may have a different prognosis compared to patients who were retained in the study, therefore contributing bias to the study. Sensitivity analyses can be conducted to estimate if the patients lost to follow-up would contribute a significant effect to the primary endpoint, however this is difficult to do with a continuous measure. We could assume all intervention patients lost to follow-up had the same change in ACQ as the mean change in ACQ in UC. However, using the last value carried forward method assumes no change, which is more conservative as UC patients had a 0.33 improvement in change in ACQ.

### 4.2.4 Sample Size, Power of the Study and Type II Error

Although power was maximized in the sample size calculation (90% power) there is still a risk of failing to reject the null hypothesis ($H_o$=no difference between the 2 groups) when it should have been rejected, a Type II error. The sample size calculation was based on a minimally clinically important difference of 0.5, 90% power and a two-tailed alpha of 0.05. From this, 19 patients per group were required. Only 40 patients completed both their 6-month RT and pharmacist visits. This still exceeds the minimum number of patients required for 90% power. Therefore, the study was adequately powered and the sample size requirements were met. A post-hoc power analysis using the same parameters as the original sample size calculation, revealed 95% power to detect a difference between the study groups ($Z_\beta$=1.91) (127).

### 4.2.5 Imbalance in Study Groups

The treatment groups appeared to be different at baseline. The groups were significantly different with regards to previous unscheduled physician visits, inhaler technique, previous pulmonary function tests and peak expiratory flow (PEF) monitoring. All unbalanced factors were controlled for in the multivariate model. Only inhaler technique significantly contributed to the model, however the overall model was still not significant.

These differences at baseline could be markers of different levels of asthma severity. As more patients in the UC group monitored PEF, these patients may have been more educated or aware of their asthma at baseline. More patients in UC had adequate inhaler technique, which may also reflect an increased level of asthma knowledge. The imbalance in previous PFT may reflect that UC patients, with a higher reported incidence of previous pulmonary function testing, were followed closer by their physician.

The goal of randomization is to produce comparable study groups, remove allocation bias and assure that statistical tests have valid significance levels (132). Randomization attempts to eliminate selection bias by making the allocation of patient to study group unpredictable. Accidental bias can occur if randomization does not achieve balance with regards to prognostic variables; this is more common in small studies (132).

There are randomization procedures available that allow for balancing of prognostic factors as recruitment is occurring during a study (adaptive randomization procedures) (132;133). Depending on the method used, patients can be allocated to treatment groups based on prognostic factors which are "imbalanced" between the study groups. The advantage is that this method protects against severe imbalances in prognostic factors. The disadvantages are that more complicated statistical analyses are required, and the process of randomization is operationally more difficult to carry out (132). It was not known prior to the start of the study that 4 factors would be significantly different after randomization. There was no specific factor that would have been considered important enough to base the entire randomization procedure around.

During study design, it was felt that stratifying randomization by site would help control for most of the important prognostic factors, and stratification can improve power in studies of small to moderate size (133). Randomization was done in blocks of 6, which allowed for the number of UC and intervention patients to be similar for each site. Random block size is often recommended in unblinded studies as this makes it even more difficult to predict the next allocation.

In summary, there were known prognostic factors that were not balanced post-randomization, and even after adjusted multivariate linear regression, there was still no difference in the change in ACQ between UC and intervention. There may be unknown prognostic factors, which cannot be controlled for in analysis that played a role in the differences between the groups. BREATHE was rigorously designed to help reduce bias, however, it is impossible to completely eliminate bias.

### 4.2.6 Properties of the ACQ and Definition of Asthma Control

The ACQ may not have been sensitive enough to detect a difference between the two groups, even if one existed. The minimally clinical important difference of the ACQ is 0.5 (134;135). In the validation study, symptomatic asthma was defined as having an ACQ > 0.5, and this corresponded to an average $FEV_1$ percent predicted of 77.2 ($\pm$18.8) (136). The baseline ACQ in our study population was 1.91 in the UC group and 1.45 in intervention; therefore indicating the study population had symptomatic asthma. Although this difference was not statistically significant at baseline, the difference approaches the minimal clinically important difference of 0.5. The change in ACQ in the intervention group approached 0.5, however there was also a greater than expected change in the usual care group. This could be due to contamination (section 4.2.1). Alternatively there may have been a Hawthorne effect (128).

The use of other outcome measures (ED visits/hospitalizations) as the primary endpoint was limited by the size of the communities as well as the structure of health-care provision within the communities. The use of the physician clinics for emergency side-stream therapy decreases the amount of ED visits that would be expected. Other studies that have measured asthma control as an endpoint have used other symptom measures such as the Global Initiative for Asthma (GINA) guidelines of asthma control or the North of England asthma symptom scale (137;138). The GINA guidelines are shown below in Table 4.1.

Table 4.1: The Global Initiative for Asthma definitions of asthma control

| | **Goals of GINA** | **Total Control** | **Well Controlled** |
|---|---|---|---|
| | | **Each week all of:** | **Each week 2 or more of:** |
| Daytime Symptoms | Minimal | None | ≤ 2 days with symptom score >1 |
| Rescue medication use | Minimal | None | Use on ≤2 days and ≤4 occasions/week |
| Morning PEF | Near normal | ≥80% predicted everyday | ≥80% predicted everyday |
| | | | ALL of: |
| Night-time awakenings | Minimal | None | None |
| Exacerbations | Minimal | None | None |
| Emergency Visits | None | None | None |
| Treatment –related adverse events | Minimal | None causing change in therapy | None causing change in therapy |

The parameters, which the GINA guidelines encompass, cover many of the same parameters as the ACQ (night-time awakenings, morning symptoms, rescue medication use). The North of England asthma symptom scale is based on 10 questions with 5 response options therefore is more closely related to the ACQ in terms of scoring.

The ACQ has some ideal components of a rating scale or questionnaire. It is highly responsive, correlates to change in other clinical measures and includes meaningful clinical information (139;140). The scaling of the ACQ includes 7 response options on a unipolar scale. This allows for the data to be treated as a continuous measure (141). Being a continuous measure, the ACQ allows for complex statistical modeling such as linear regression modeling and can also be more responsive to change than a categorical measure such as the GINA guidelines. By increasing the number of responses, the variance of the score increases, and therefore the responsiveness increases (142). The summated rating helps to decrease measurement error (142). The properties of the ACQ are ideal for use as a clinical outcome measure in a clinical trial. The time allowed for the study may not have been enough to measure change. Given the multiple components of the intervention and coordination of care by all primary caregivers, it takes considerable time to allow the intervention to invoke a change in ACQ. This may have required more follow-up time. Therefore, even if the ACQ properties were sufficient to measure that change, the time allowed for follow-up may not have been enough to develop change.

### 4.2.7 Definition of High-risk

The study population may not have been as high-risk as we had originally anticipated. High-risk was defined as having an ED visit / hospitalization in the previous 12 months or using >2 canisters of inhaled beta-2 agonist over 6 months. The majority of patients were admitted into the study for having met the beta-2 agonist overuse criteria (over 90%). There is no standard definition in the literature of beta-2 agonist overuse. The Canadian Asthma Consensus Guidelines define control as using less than 4 doses in one week (32). The pharmacists were to assess, at baseline visit, whether the patient was actually using their inhaler more than three times per week. Some patients may have appeared to use more than 2 canisters over 6 months, but were actually not using their inhaler this often. These patients may have lost inhalers, or "stock-piled" inhalers in various locations to have a reliever on-hand when required. These patients should have been identified at screening and then excluded from the study, as they truly did not meet the entry criteria for overuse. Perhaps, as beta-2 agonist overuse is only one component of control, as a single indicator of control it does not adequately reflect a high-risk population. As an alternative marker of high-risk status, previous courses of oral steroids may be a more sensitive marker of control. In the regression analysis, previous courses of oral steroids significantly predicted future courses of oral steroids.

The baseline scores (1.45 – 1.91) of the ACQ do indicate that the sample captured was poorly controlled. There is no published data correlating ACQ scores with risk for other events.

### 4.2.8 Summary of Primary Outcome

In summary, there was no difference between UC and intervention in terms of asthma control. The main reasons to explain why no difference between groups was observed include contamination of the study group, poor application of the intervention and significant losses-to-follow-up.

## 4.3 Secondary Outcomes

As specified in the study protocol, secondary analysis included comparison of inhaled corticosteroid use, change in $FEV_1$, comparison of courses of oral steroids, and ED visits and hospitalizations.

### 4.3.1 Inhaled Corticosteroid Use

The baseline use of inhaled corticosteroids was quite high, with 72% of the overall study population receiving them. This is higher than what was found in the ASTHMA study and other published literature (58;143). So, although patients were considered high-risk by our inclusion criteria, there were prescribed appropriate therapy the majority of the time. By the end of the study, 83% of the intervention group was on inhaled steroid. Although there was no statistically significant difference in inhaled corticosteroid use between UC and intervention at 6 months, the usage of inhaled corticosteroids increased in both groups. Whether this increase is due to the intervention or other cointerventions is uncertain, but is a positive result of the study. As the UC group also increased their inhaled corticosteroid use (82% at the end of the study), they may have been some Hawthorne effect from just being enrolled in the study. As a result, both study groups benefited from enrollment in the study in terms of appropriate medication use.

### 4.3.2 Change in $FEV_1$

As an objective measure of asthma control, change in $FEV_1$ was included in the analysis. As with the other outcome measures, there was no difference between the groups with regards to change in $FEV_1$. The change in $FEV_1$ was very small in both study groups, with a 3% change in UC and 0.6% change in intervention. It was not anticipated that a large difference in $FEV_1$ would be measured. It is an objective outcome measure and therefore was included in the analysis.

Symptoms are not highly correlated with lung function (144). Even if there was a measured difference in ACQ, there may not have been a corresponding improvement in lung function. The lung function measurements in BREATHE were based on one time measurements. As asthma is characterized by reversible airflow obstruction, the $FEV_1$ can be quite variable within one day (diurnal variation) (12). It may be more accurate to have repeated measurements at different times of the day; however, this is more cumbersome to do. Many asthma clinical trials specify at what time $FEV_1$ should be done to be consistent within the population. This was difficult to do in BREATHE, as there was not a dedicated study RT or the resources available to bring patients in at specific times. The goal was to apply a model in a real-world setting, therefore making it impossible to rigidly plan $FEV_1$ measurements to be done in all patients, at the same time of the day.

### 4.3.3 Courses of Oral Steroids

In the logistic regression model containing previous courses of oral steroids, the difference between intervention and control approached statistical significance (OR 0.35, 95% CI 0.10-1.26, p=0.08). This endpoint, which is an alternative marker of control, is not captured in the ACQ. Courses of oral steroids reflect asthma exacerbations that may or may not have required ED visit.

A confounding factor with using courses of oral steroid is that intervention patients may have been prescribed steroids (to keep for emergency use) as part of their WAP (Appendix 3). Therefore, they may not have actually required the oral steroids for an exacerbation, but had them on hand if required. If this occurred in just 1 intervention patient, the courses of oral steroids between the study groups would have been statistically significantly different (p=0.04). This is a common practice with the use of WAP and may be a confounding factor with the results. By investigating some of the other recommendations made at follow-up, pharmacists did recommend to have oral steroid on hand in some cases.

This finding is a positive outcome of the study and is clinically significant. The reduction of use of oral steroids is an outcome often used in clinical trials as it reflects urgent care needs. This result means that patients are prevented from proceeding to the ED or hospital, which has implications on health-care utilization and direct costs associated with asthma.

#### 4.3.4 ED visits and Hospitalizations

When the study was originally designed, the primary outcome measure was to compare ED visits and hospitalizations. However, after discussions with the local physicians and pharmacists it was determined that this might not capture all acute asthma-related events, as patients often just proceed to their physicians office (an unscheduled physician visit). Moreover, the sample size required for this endpoint is higher. After these discussions, it was decided to use an endpoint that required a smaller population and may more accurately reflect the level of control, hence the selection of the ACQ.

Now that data analysis is complete, it is apparent that the choice of ED visits / hospitalizations would have been difficult to show a difference between the 2 groups. With only a 17% event rate, a total of 241 patients would have been required to show a 50% difference between the 2 groups (two-tailed alpha=0.05, beta=80%). It took 1.5 years to recruit the 70 patients included in this study, and would have taken over 5 years (assuming the same recruitment rate) to obtain the required sample size. From the literature, the anticipated event rate for ED visits and hospitalizations was 18 - 28% (2). The event rate in the BREATHE study is slightly below that, possibly reflecting the use of physician offices for emergency care.

Even though patients in intervention were being followed closer, there should be no concern with regards to detection bias, as this data was collected via subjective means. However, some asthma studies have shown that after patients received a WAP they had more ED visits, compared to controls, as they are more aware of their symptoms and deterioration, and when to seek emergency assistance (145).

## 4.4 Additional Analyses

The primary and secondary outcomes were analyzed and reported using intention-to-treat analysis. The intention-to-treat principle preserves the power of randomization (146). Per-protocol or on-treatment analysis introduces bias by creating non-comparable groups. With this in mind, secondary analyses were conducted.

### 4.4.1 Analysis of Patients with Complete Follow-up

Patients lost-to-follow-up may have prognostic differences from the patients who are retained in the study. Therefore, any positive results found from an analysis of only the patients who completed follow-up have to be interpreted cautiously. A comparison of all patients who completed the 6-month RT follow-up was done and there was no significant difference between intervention and usual care. As no difference was found, follow-up may not have been an important component of the intervention.

### 4.4.2 Analysis of Patients with a WAP

We also compared patients in intervention who had a WAP to intervention who did not have a WAP. As this analysis is a type of sub-group analysis, the results should be interpreted cautiously. It was done as an exploratory analysis to determine if one component of the intervention made a difference. There was a significant difference between intervention patients who received a WAP and those who did not (p<0.001). Intervention patients who received a WAP had a mean change in ACQ of 0.55. Patients in intervention who did not have a WAP did poorer than the UC patients (Figure 3.13). As the UC patients appeared to have done better than the intervention patients who did not receive a WAP, there may have been some WAP education (particularly by the RT) to the UC patients. This contamination is difficult to ascertain, as there was no data collected in UC patients regarding WAP education.

The patients who did not receive a WAP may be systematically different from the other intervention patients and UC patients, therefore it is difficult to draw many conclusions from this analysis. However, it is promising that one component of the intervention may have a significant effect on outcomes.

### 4.4.3 Before-After Design

Many pharmacy practice studies employ a before-after design (147;148). If we had used a before-after design with BREATHE, the change in ACQ from baseline to 6-months is statistically significant (p=0.006). This stresses the importance of having a control group. By using a before-after design we would have erroneously concluded that the intervention significantly improved asthma control in high-risk patients. The use of a control group and randomized design allows for derivation of a causal inference regarding treatment and outcome.

## 4.5 External Validity and Other Limitations

There are a number of limitations with the study. Many of these limitations are discussed in Section 4.2 as explanations for the primary outcome. The limitations included in this section are not dependent on the outcomes of the study.

The generalizability (external validity) of this study to urban centres may be limited. This study was specifically designed for a rural setting, with the thought of applying the model to other chronic disease states. It would be difficult to apply this model to an urban setting given the multi-disciplinary, community nature of the design. In the communities of Hinton and Edson it was feasible to involve all the physicians as there are few of them. Involvement of the RT was also practical as there is only one shared between Hinton and Edson hospitals. By using a rural setting we had the advantage of including these primary-health care providers not only in the intervention, but also the design and implementation of the study. In an urban setting, it would be very difficult to include all physicians and RTs in study design, implementation and application of the intervention.

There are also issues regarding generalizability to pharmacy practice. Clearly, not all pharmacists are motivated enough to get involved in the primary-care of their patients. Even in a relatively controlled environment of a study, we had difficulty encouraging pharmacists to administer the intervention, even after intense training and support. This is consistent with other pharmacy practice studies (149;150). Pharmacists at site 2 and site 5 were consistently offered supports to help in the administration of the intervention, however we know that these sites had both poor follow-up and application of the intervention. Given a normal, uncontrolled environment where there are no external supports, the quality of care would be considerably less. Evidently, pharmacists who believe in the progressive nature of their profession require little external motivation to become involved with patient care. This study would be applicable to these pharmacists. However, pharmacists who maintain a primarily dispensing role in patient care would have less to gain from pharmacy-practice based research.

Patients, who were more aware of their condition and had more interest in achieving asthma control, may have selected themselves out of the general population to be involved in the study (volunteer bias). These patients would consequently be more motivated and likely to have a change in asthma control.

This model can only be applied to adult asthma patients. Education programs for children are much different, given different reading levels and comprehension. Also the data to support WAP in children is much different, as PEF monitoring does not have the same literature to support it in a pediatric population. Older patients ($\geq$55 years of age) were excluded from the study to reduce contamination of the study population with COPD patients. There is no reason to suggest, however, that this program would not have the same effect on elderly patients as the patients included in this study.

## 4.6 Unique Design Aspects

### 4.6.1 Rural, Community-Based

Both Edson and Hinton are rural settings (Edson population 7800, Hinton population 9400), 200 and 300 kilometres from the nearest tertiary care facilities in Edmonton. This offered a "closed" area in which to evaluate the intervention. Most patients are treated and followed up within the same town where they live and there is little involvement of any larger surrounding cities.

The primary benefit of community-based approaches to health-care management is the involvement of all major primary-care providers and an awareness of the community. The transition of care from one provider to another requires the passage of patient-related knowledge. This can be done from provider to provider or via the patient. Having patients involved in this knowledge transfer encourages them to take ownership of their disease. The involvement of the community promotes a positive environment for such interventions to occur.

Given the unique environment of rural communities, this model offers an alternative management system for patients, which involves a broader health-care concept.

### 4.6.2 Multidisciplinary

The physicians in these communities, as well as the hospital-based RT were involved in development of the protocol and WAP, along with the community and hospital pharmacists. Physicians approved the WAP for initiation by the pharmacists. Given the multidisciplinary nature of the intervention, both RT and physicians were integral in the provision of the intervention. Referral to other health care professionals that can offer beneficial education and therapy to patients is unique in pharmaceutical care trials.

### 4.6.3 Pharmacist-Initiated

Patients were primarily identified based on refill information that is available and reviewed with prescription refills. This has tremendous potential as an entry point for patients into the health care system. Physicians are often unaware of the amount of beta-agonist reliever being used by their patients and therefore may not be aware of the patient's asthma control. Beta-agonist overuse provides an objective measure of control, as other methods of control assessment, such as self-reports of symptoms alone, have been shown to underestimate true determination of asthma severity (151). This referral mechanism allows the physician to be aware of an important component in determining asthma control.

### 4.6.4 High-risk Patients

Patients included in the study are at higher-risk of morbidity (152;153). Therefore, this program was targeted at affecting those patients who are the highest users of the health-care system in terms of asthma patients. Patients who present to ED for an asthma exacerbation, often do not follow-up with their physician, and this program offered a system that attempts to overcome this care gap (58).

## 4.7 Implications and Future Research

Although the study results would be considered neutral, there were some positive outcomes from the study.

### 4.7.1 Rural Health Issues

The focus of the study on rural health issues is novel, as most randomized controlled trials occur in larger centres, with a strong influence from academia. Although the University of Alberta was primarily responsible for the design and implementation of the study protocol, the intervention itself was carried out by local investigators, none of who had been previously involved in research. Rural health issues are different from those in urban centres, given the different structure of health-care and have been the focus of new research opportunities funded by agencies such as CIHR (154).

In Canada, approximately 1/3 of the population lives in rural communities. The health-care structure needs to include policy development that considers the significant number of people residing in rural Canada. Research suggests that the health status of the rural-dwelling population may be inferior to people living in urban settings; therefore, there are opportunities to improve health status of people living in rural communities (155). Accessibility to health services has an impact on the health status of rural dwellers. As pharmacists are highly accessible, community-based, health-care providers, their role in rural health needs further exploration.

The disadvantages of conducting rural health research include remote project management, limited population from which to derive your sample and less research experience of on-site investigators. However, given the novel opportunities to involve communities in multi-disciplinary strategies in relatively "closed" areas, many of these disadvantages can be overcome with study design and appropriate training.

### 4.7.2 Application to Other Disease States

The model of the BREATHE study could be applied to other disease states. The BREATHE design was based on the previously published SCRIP study, which was a study of cardiovascular risk (156;157). Other disease states which we are being considered for study with a similar methodology, include hypertension and osteoporosis. The challenges encountered in the BREATHE study will help strengthen the interventions in future studies, as there will be similar obstacles to overcome, with regards to recruitment, losses to follow-up and contamination.

The usefulness of a pharmacist as an entrance point into the health-care system does not have to be limited to asthma. Patients visit their pharmacist far more frequently than their physician and therefore provide an excellent opportunity for community-based disease management. The accessibility of the pharmacist to the patient allows them to often be the first point of contact in the health-care system. There is published evidence that demonstrate that pharmacist-led management programs improve outcomes (158). With further evidence, the validity of using pharmacists as an integral part of primary health-care management will be strengthened and applied to primary health-care reform.

### 4.7.3 Qualitative Study of Pharmacist Investigators

The different reasons for what motivated the pharmacists to be involved in the project are unclear. For some of the pharmacists, it appeared they were interested in the betterment of the profession, and other pharmacists may have been more interested in the marketing of a project to help bring in new clientele. Most of this information is from anecdotal report and has not been further explored. Since involvement of the sites varied so significantly it would be interesting to determine what factors influenced the pharmacists involvement. Many of the sites had staffing constraints due to the pharmacist shortage, and this was an often cited reason for poor recruitment and follow-up. However, the site which recruited the most patients (site 1) also experienced a pharmacist shortage over the course of the study. The factors influencing involvement would be useful for future pharmacist practice studies as it would assist in selection of pharmacists and sites. By identifying these factors, it would also help in determining how to motivate pharmacist investigators during the study. Weinberger, et al published an article on their challenges with pharmacy-practice based research and how to identify and overcome these issues (150). This could be expanded on with similar research from other practice-based studies. Focus groups with the pharmacist investigators from BREATHE would help elucidate some of these barriers and assist in the selection of investigators, and in the design and implementation of future pharmacy-practice based research.

### 4.8 Conclusions

In adult patients with a history of asthma, there was no difference in asthma control after a 6-month assessment, education and referral program, as compared to usual care. On average, patients in both study groups improved their level of asthma control. There was an increase in the amount of inhaled corticosteroids prescribed to both UC and intervention. There was a trend towards reduced use of oral steroids in intervention patients.

Although there were no differences found between the study groups, there were a number of positive outcomes of the study. The multi-disciplinary nature of the study was unlike other community-pharmacy interventions. The involvement of the physicians and RT prior to initiation of the study allowed for modification and refinement of the study design. This program allowed academics and primary health-care providers from a rural setting to work together to undertake a research project.

This model of pharmacist-initiated, primary health-care program requires further study in other chronic diseases.

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# Appendix 1: Recruitment Script

Hi _(participant name)______, this is __(pharmacist name)__ from __(pharmacy name)_. I am calling regarding your asthma control. We are currently involved in a program working with local physicians and the hospital to investigate ways to better control asthma. The study involves education about asthma, testing of your lung function and follow-up for 6 months. The benefits are potentially better control of your asthma and the costs are relatively low, other than the time required to participate. We have an information sheet that describes the study and what would be required from your participation. It would take about 15 minutes to go over this to see if you want to be involved and everything is strictly confidential. Your participation in the study will not identify you as an individual patient, and you will be free to withdraw from the study at any time with no effect on your care or the services you receive. Would you like to make an appointment to come in and discuss this? (if yes, arrange time; if no, thank them for their time).

# Appendix 2: Consent Forms

UNIVERSITY OF ALBERTA

## Patient Information Sheet

**Title of Research Study:** Better Respiratory Education and Asthma Treatment in Hinton and Edson (BREATHE)

**Principal Investigator:** Dr. Ross T. Tsuyuki

**Co-Investigator(s):** Teri Charrois, Carolyn Nilsson, Dr. Don Sin, Dr. Stephen Newman, Dr. Ambikaipakan Senthilselvan

**Background:** Asthma is a common condition, affecting up to 10% of Albertans. It causes symptoms of shortness of breath and cough, so that people with asthma are less active. It is also a major cause of missed school or work days. Our previous research has shown that many patients with asthma could have better asthma control when they have better knowledge of asthma and medicine use.

**Purpose:** The purpose of this study is to find out if your pharmacist can help improve your asthma symptoms. It is quick and easy to get answers about asthma and asthma medicines from your pharmacist. Two groups of people will be compared. The first group of people with asthma (Group A) will learn about asthma from their pharmacist and respiratory therapist. Their family doctor will check their asthma medicines. The second group (Group B) will have usual pharmacy and doctor care. This group of people will still get the care that they need from the pharmacist and family doctor. This study is part of graduate thesis work.

Procedures: This is what will happen if you agree to take part in this study:

a) There are two reasons why you are being asked to be part of this study. One reason is that you may have been to the hospital or emergency department for your asthma sometime in the last year. This may mean that your asthma could be better controlled. The second reason is that you have been taking asthma medicines sometime during the last 6 months
b) The first time you come to the pharmacy, we will make sure that you fit into the study. We will ask you if you want to be part of the study and then have you sign a consent form. This should take about 20 minutes.
c) There is an asthma questionnaire (the Asthma Control Questionnaire) that we will ask you to fill out. This should take about 10 minutes. Everything you write down will be kept private.
d) The study-coordinating centre will randomly decide which group you will go into. This is like flipping a coin to make the decision. Neither you nor the investigator can choose which group you are assigned to. This is done so that the study program is given a fair test.
e) The study will last 6 months.
f) You will be asked to sign a consent that will allow the Hinton or Edson General Hospital to provide the study with dates of any time you have had to go to the hospital because of your asthma.
g) What happens for the rest of the study will depend on which group you get put into.

If you are in Group A, you will receive teaching about your asthma symptoms, medicine and treatment plan. You will be asked to have a lung function test done now, and then again in 2 months and 6 months from now. You will be contacted either by telephone or in person in 2 weeks, and then 1, 2, 4 and 6 months from now, to review your medicines and asthma symptoms. We will ask if you have had to go to the hospital or emergency for your asthma. Each phone call should take about 10 minutes of your time. Your family doctor will be told that you are in this study. You may be asked to make an appointment with him/her for

# Appendix 3: Written Action Plan

BREATHE

# Asthma Action Plan

**Reliever Medication:** ____________________ **Preventor Medication:** ____________________

| | | |
|---|---|---|
| **GREEN ZONE**<br>• I do not wheeze, cough or have trouble breathing with activity.<br>• I do not wake at night because of my asthma.<br>• I use my reliever medicine 4 times per week or less, except before exercise.<br>• ____________________<br>Peak flow is above (80%) ________ | **YELLOW ZONE**<br>• I wheeze, cough or have trouble breathing that goes away when I take my reliever medicine.<br>• I have a cold or flu.<br>• I wheeze, cough or have trouble breathing at night that goes away when I take my reliever medicine.<br>• I use my reliever medicine once per day.<br>• ____________________<br>Peak flow is above (60-80%) ________ | [redacted] |
| **ACTIONS**<br>• Take preventor medicine __________ _____ puffs _____ times per day.<br>• Take medicine ______________ _____ puffs/pills _____ times per day.<br>• Take reliever medicine __________ 1-2 puffs every 4-6 hours as needed.<br>• Avoid triggers of asthma.<br>• ____________________ | **ACTIONS**<br>• Take preventor medicine __________ _____ puffs _____ times per day.<br>• Take medicine ______________ _____ puffs/pills_____ times per day.<br>• Take reliever medicine __________ 1-2 puffs every 4-6 hours as needed.<br>• Avoid triggers of asthma.<br>• ____________________ | |